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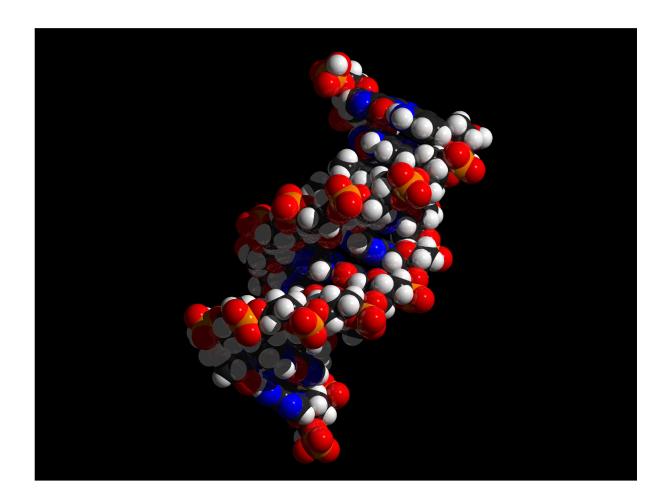
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OU Human Physiology: Chemistry Refresher Introduction class="introduction" Human DNA

Human DNA
is described
as a double
helix that
resembles a
molecular
spiral
staircase. In
humans the
DNA is
organized into
46
chromosomes

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Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the fundamental composition of matter
- Identify the three subatomic particles
- Identify the four most abundant elements in the body
- Explain the relationship between an atom's number of electrons and its relative stability
- Distinguish between ionic bonds, covalent bonds, and hydrogen bonds
- Explain how energy is invested, stored, and released via chemical reactions, particularly those reactions that are critical to life
- Explain the importance of the inorganic compounds that contribute to life, such as water, salts, acids, and bases

Compare and contrast the four important classes of organic (carbon-based) compounds—proteins, carbohydrates, lipids and nucleic acids
 —according to their composition and functional importance to human life

The smallest, most fundamental material components of the human body are basic chemical elements. In fact, chemicals called nucleotide bases are the foundation of the genetic code with the instructions on how to build and maintain the human body from conception through old age. There are about three billion of these base pairs in human DNA.

Human chemistry includes organic molecules (carbon-based) and biochemicals (those produced by the body). Human chemistry also includes elements. In fact, life cannot exist without many of the elements that are part of the earth. All of the elements that contribute to chemical reactions, to the transformation of energy, and to electrical activity and muscle contraction—elements that include phosphorus, carbon, sodium, and calcium, to name a few—originated in stars.

These elements, in turn, can form both the inorganic and organic chemical compounds important to life, including, for example, water, glucose, and proteins. This chapter begins by examining elements and how the structures of atoms, the basic units of matter, determine the characteristics of elements by the number of protons, neutrons, and electrons in the atoms. The chapter then builds the framework of life from there.

OU Human Physiology: Elements and Atoms: The Building Blocks of Matter

By the end of this section, you will be able to:

- Discuss the relationships between matter, mass, elements, compounds, atoms, and subatomic particles
- Distinguish between atomic number and mass number
- Identify the key distinction between isotopes of the same element
- Explain how electrons occupy electron shells and their contribution to an atom's relative stability

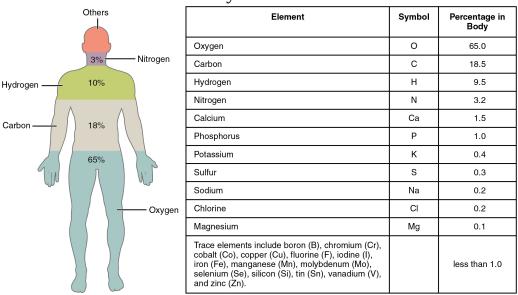
The substance of the universe—from a grain of sand to a star—is called **matter**. Scientists define matter as anything that occupies space and has mass. An object's mass and its weight are related concepts, but not quite the same. An object's mass is the amount of matter contained in the object, and the object's mass is the same whether that object is on Earth or in the zero-gravity environment of outer space. An object's weight, on the other hand, is its mass as affected by the pull of gravity. Where gravity strongly pulls on an object's mass its weight is greater than it is where gravity is less strong. An object of a certain mass weighs less on the moon, for example, than it does on Earth because the gravity of the moon is less than that of Earth. In other words, weight is variable, and is influenced by gravity. A piece of cheese that weighs a pound on Earth weighs only a few ounces on the moon.

Elements and Compounds

All matter in the natural world is composed of one or more of the 92 fundamental substances called elements. An **element** is a pure substance that is distinguished from all other matter by the fact that it cannot be created or broken down by ordinary chemical means. While your body can assemble many of the chemical compounds needed for life from their constituent elements, it cannot make elements. They must come from the environment. A familiar example of an element that you must take in is calcium (Ca⁺⁺). Calcium is essential to the human body; it is absorbed and used for a number of processes, including strengthening bones. When you consume dairy products your digestive system breaks down the food into

components small enough to cross into the bloodstream. Among these is calcium, which, because it is an element, cannot be broken down further. The elemental calcium in cheese, therefore, is the same as the calcium that forms your bones. Some other elements you might be familiar with are oxygen, sodium, and iron. The elements in the human body are shown in [link], beginning with the most abundant: oxygen (O), carbon (C), hydrogen (H), and nitrogen (N). Each element's name can be replaced by a one- or two-letter symbol; you will become familiar with some of these during this course. All the elements in your body are derived from the foods you eat and the air you breathe.

Elements of the Human Body



The main elements that compose the human body are shown from most abundant to least abundant.

In nature, elements rarely occur alone. Instead, they combine to form compounds. A **compound** is a substance composed of two or more elements joined by chemical bonds. For example, the compound glucose is an important body fuel. It is always composed of the same three elements: carbon, hydrogen, and oxygen. Moreover, the elements that make up any given compound always occur in the same relative amounts. In glucose,

there are always six carbon and six oxygen units for every twelve hydrogen units. But what, exactly, are these "units" of elements?

Atoms and Subatomic Particles

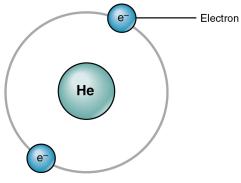
An **atom** is the smallest quantity of an element that retains the unique properties of that element. In other words, an atom of hydrogen is a unit of hydrogen—the smallest amount of hydrogen that can exist. As you might guess, atoms are almost unfathomably small. The period at the end of this sentence is millions of atoms wide.

Atomic Structure and Energy

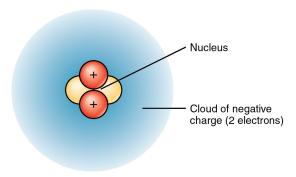
Atoms are made up of even smaller subatomic particles, three types of which are important: the **proton**, **neutron**, and **electron**. The number of positively-charged protons and non-charged ("neutral") neutrons, gives mass to the atom, and the number of each in the nucleus of the atom determine the element. The number of negatively-charged electrons that "spin" around the nucleus at close to the speed of light equals the number of protons. An electron has about 1/2000th the mass of a proton or neutron.

[link] shows two models that can help you imagine the structure of an atom —in this case, helium (He). In the planetary model, helium's two electrons are shown circling the nucleus in a fixed orbit depicted as a ring. Although this model is helpful in visualizing atomic structure, in reality, electrons do not travel in fixed orbits, but whiz around the nucleus erratically in a so-called electron cloud.

Two Models of Atomic Structure



(a) Planetary model



(b) Electron cloud model

- (a) In the planetary model, the electrons of helium are shown in fixed orbits, depicted as rings, at a precise distance from the nucleus, somewhat like planets orbiting the sun.
- (b) In the electron cloud model, the electrons of carbon are shown in the variety of locations they would have at different distances from the nucleus over time.

An atom's protons and electrons carry electrical charges. Protons, with their positive charge, are designated p⁺. Electrons, which have a negative charge,

are designated e⁻. An atom's neutrons have no charge: they are electrically neutral. Just as a magnet sticks to a steel refrigerator because their opposite charges attract, the positively charged protons attract the negatively charged electrons. This mutual attraction gives the atom some structural stability. The attraction by the positively charged nucleus helps keep electrons from straying far. The number of protons and electrons within a neutral atom are equal, thus, the atom's overall charge is balanced.

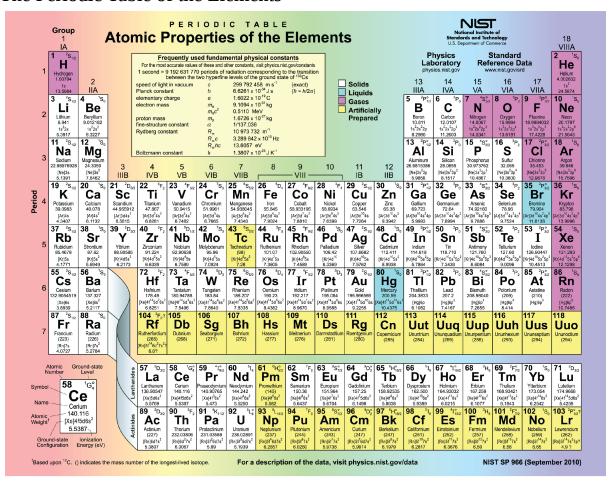
Atomic Number and Mass Number

An atom of carbon is unique to carbon, but a proton of carbon is not. One proton is the same as another, whether it is found in an atom of carbon, sodium (Na), or iron (Fe). The same is true for neutrons and electrons. So, what gives an element its distinctive properties—what makes carbon so different from sodium or iron? The answer is the unique quantity of protons each contains. Carbon by definition is an element whose atoms contain six protons. No other element has exactly six protons in its atoms. Moreover, *all* atoms of carbon, whether found in your liver or in a lump of coal, contain six protons. Thus, the **atomic number**, which is the number of protons in the nucleus of the atom, identifies the element. Because an atom usually has the same number of electrons as protons, the atomic number identifies the usual number of electrons as well.

In their most common form, many elements also contain the same number of neutrons as protons. The most common form of carbon, for example, has six neutrons as well as six protons, for a total of 12 subatomic particles in its nucleus. An element's **mass number** is the sum of the number of protons and neutrons in its nucleus. So the most common form of carbon's mass number is 12. (Electrons have so little mass that they do not appreciably contribute to the mass of an atom.) Carbon is a relatively light element. Uranium (U), in contrast, has a mass number of 238 and is referred to as a heavy metal. Its atomic number is 92 (it has 92 protons) but it contains 146 neutrons; it has the most mass of all the naturally occurring elements.

The **periodic table of the elements**, shown in [link], is a chart identifying the 92 elements found in nature, as well as several larger, unstable elements discovered experimentally. The elements are arranged in order of their atomic number, with hydrogen and helium at the top of the table, and the more massive elements below. The periodic table is a useful device because for each element, it identifies the chemical symbol, the atomic number, and the mass number, while organizing elements according to their propensity to react with other elements. The number of protons and electrons in an element are equal. The number of protons and neutrons may be equal for some elements, but are not equal for all.

The Periodic Table of the Elements



(credit: R.A. Dragoset, A. Musgrove, C.W. Clark, W.C. Martin)

Note:

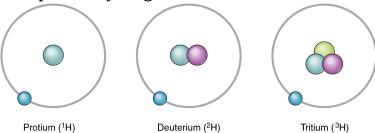


Visit this <u>website</u> to view the periodic table. In the periodic table of the elements, elements in a single column have the same number of electrons that can participate in a chemical reaction. These electrons are known as "valence electrons." For example, the elements in the first column all have a single valence electron, an electron that can be "donated" in a chemical reaction with another atom. What is the meaning of a mass number shown in parentheses?

Isotopes

Although each element has a unique number of protons, it can exist as different isotopes. An **isotope** is one of the different forms of an element, distinguished from one another by different numbers of neutrons. The standard isotope of carbon is ¹²C, commonly called carbon twelve. ¹²C has six protons and six neutrons, for a mass number of twelve. All of the isotopes of carbon have the same number of protons; therefore, ¹³C has seven neutrons, and ¹⁴C has eight neutrons. The different isotopes of an element can also be indicated with the mass number hyphenated (for example, C-12 instead of ¹²C). Hydrogen has three common isotopes, shown in [link].

Isotopes of Hydrogen



Protium, designated ¹H, has one proton and no neutrons. It is by far the most abundant isotope of hydrogen in nature. Deuterium, designated ²H, has one proton and one neutron. Tritium, designated ³H, has two neutrons.

An isotope that contains more than the usual number of neutrons is referred to as a heavy isotope. An example is ¹⁴C. Heavy isotopes tend to be unstable, and unstable isotopes are radioactive. A **radioactive isotope** is an isotope whose nucleus readily decays, giving off subatomic particles and electromagnetic energy. Different radioactive isotopes (also called radioisotopes) differ in their half-life, the time it takes for half of any size sample of an isotope to decay. For example, the half-life of tritium—a radioisotope of hydrogen—is about 12 years, indicating it takes 12 years for half of the tritium nuclei in a sample to decay. Excessive exposure to radioactive isotopes can damage human cells and even cause cancer and birth defects, but when exposure is controlled, some radioactive isotopes can be useful in medicine. For more information, see the Career Connections.

Note:

Career Connection

Interventional Radiologist

The controlled use of radioisotopes has advanced medical diagnosis and treatment of disease. Interventional radiologists are physicians who treat disease by using minimally invasive techniques involving radiation. Many conditions that could once only be treated with a lengthy and traumatic operation can now be treated non-surgically, reducing the cost, pain, length of hospital stay, and recovery time for patients. For example, in the past, the only options for a patient with one or more tumors in the liver were surgery and chemotherapy (the administration of drugs to treat cancer). Some liver tumors, however, are difficult to access surgically, and others

could require the surgeon to remove too much of the liver. Moreover, chemotherapy is highly toxic to the liver, and certain tumors do not respond well to it anyway. In some such cases, an interventional radiologist can treat the tumors by disrupting their blood supply, which they need if they are to continue to grow. In this procedure, called radioembolization, the radiologist accesses the liver with a fine needle, threaded through one of the patient's blood vessels. The radiologist then inserts tiny radioactive "seeds" into the blood vessels that supply the tumors. In the days and weeks following the procedure, the radiation emitted from the seeds destroys the vessels and directly kills the tumor cells in the vicinity of the treatment.

Radioisotopes emit subatomic particles that can be detected and tracked by imaging technologies. One of the most advanced uses of radioisotopes in medicine is the positron emission tomography (PET) scanner, which detects the activity in the body of a very small injection of radioactive glucose, the simple sugar that cells use for energy. The PET camera reveals to the medical team which of the patient's tissues are taking up the most glucose. Thus, the most metabolically active tissues show up as bright "hot spots" on the images ([link]). PET can reveal some cancerous masses because cancer cells consume glucose at a high rate to fuel their rapid reproduction.

PET Scan



PET highlights areas in the body where there is relatively high glucose use, which is characteristic of cancerous tissue. This PET scan shows sites of the spread of a large primary tumor to other sites.

The Behavior of Electrons

In the human body, atoms do not exist as independent entities. Rather, they are constantly reacting with other atoms to form and to break down more complex substances. To fully understand anatomy and physiology you must grasp how atoms participate in such reactions. The key is understanding the behavior of electrons.

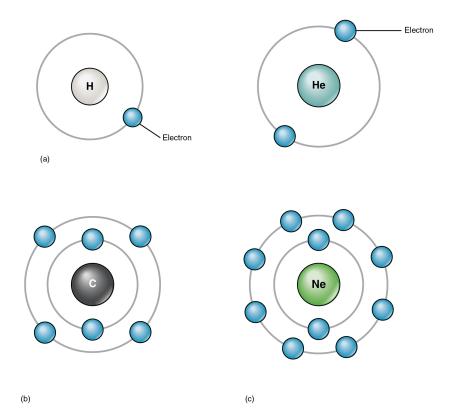
Although electrons do not follow rigid orbits a set distance away from the atom's nucleus, they do tend to stay within certain regions of space called

electron shells. An **electron shell** is a layer of electrons that encircle the nucleus at a distinct energy level.

The atoms of the elements found in the human body have from one to five electron shells, and all electron shells hold eight electrons except the first shell, which can only hold two. This configuration of electron shells is the same for all atoms. The precise number of shells depends on the number of electrons in the atom. Hydrogen and helium have just one and two electrons, respectively. If you take a look at the periodic table of the elements, you will notice that hydrogen and helium are placed alone on either sides of the top row; they are the only elements that have just one electron shell ([link]). A second shell is necessary to hold the electrons in all elements larger than hydrogen and helium.

Lithium (Li), whose atomic number is 3, has three electrons. Two of these fill the first electron shell, and the third spills over into a second shell. The second electron shell can accommodate as many as eight electrons. Carbon, with its six electrons, entirely fills its first shell, and half-fills its second. With ten electrons, neon (Ne) entirely fills its two electron shells. Again, a look at the periodic table reveals that all of the elements in the second row, from lithium to neon, have just two electron shells. Atoms with more than ten electrons require more than two shells. These elements occupy the third and subsequent rows of the periodic table.

Electron Shells



Electrons orbit the atomic nucleus at distinct levels of energy called electron shells. (a) With one electron, hydrogen only half-fills its electron shell. Helium also has a single shell, but its two electrons completely fill it. (b) The electrons of carbon completely fill its first electron shell, but only half-fills its second. (c) Neon, an element that does not occur in the body, has 10 electrons, filling both of its electron shells.

The factor that most strongly governs the tendency of an atom to participate in chemical reactions is the number of electrons in its valence shell. A **valence shell** is an atom's outermost electron shell. If the valence shell is full, the atom is stable; meaning its electrons are unlikely to be pulled away from the nucleus by the electrical charge of other atoms. If the valence shell is not full, the atom is reactive; meaning it will tend to react with other

atoms in ways that make the valence shell full. Consider hydrogen, with its one electron only half-filling its valence shell. This single electron is likely to be drawn into relationships with the atoms of other elements, so that hydrogen's single valence shell can be stabilized.

All atoms (except hydrogen and helium with their single electron shells) are most stable when there are exactly eight electrons in their valence shell. This principle is referred to as the octet rule, and it states that an atom will give up, gain, or share electrons with another atom so that it ends up with eight electrons in its own valence shell. For example, oxygen, with six electrons in its valence shell, is likely to react with other atoms in a way that results in the addition of two electrons to oxygen's valence shell, bringing the number to eight. When two hydrogen atoms each share their single electron with oxygen, covalent bonds are formed, resulting in a molecule of water, H₂O.

In nature, atoms of one element tend to join with atoms of other elements in characteristic ways. For example, carbon commonly fills its valence shell by linking up with four atoms of hydrogen. In so doing, the two elements form the simplest of organic molecules, methane, which also is one of the most abundant and stable carbon-containing compounds on Earth. As stated above, another example is water; oxygen needs two electrons to fill its valence shell. It commonly interacts with two atoms of hydrogen, forming H_2O . Incidentally, the name "hydrogen" reflects its contribution to water (hydro-= "water"; -gen = "maker"). Thus, hydrogen is the "water maker."

Chapter Review

The human body is composed of elements, the most abundant of which are oxygen (O), carbon (C), hydrogen (H) and nitrogen (N). You obtain these elements from the foods you eat and the air you breathe. The smallest unit of an element that retains all of the properties of that element is an atom. But, atoms themselves contain many subatomic particles, the three most important of which are protons, neutrons, and electrons. These particles do not vary in quality from one element to another; rather, what gives an element its distinctive identification is the quantity of its protons, called its atomic number. Protons and neutrons contribute nearly all of an atom's

mass; the number of protons and neutrons is an element's mass number. Heavier and lighter versions of the same element can occur in nature because these versions have different numbers of neutrons. Different versions of an element are called isotopes.

The tendency of an atom to be stable or to react readily with other atoms is largely due to the behavior of the electrons within the atom's outermost electron shell, called its valence shell. Helium, as well as larger atoms with eight electrons in their valence shell, is unlikely to participate in chemical reactions because they are stable. All other atoms tend to accept, donate, or share electrons in a process that brings the electrons in their valence shell to eight (or in the case of hydrogen, to two).

Glossary

atom

smallest unit of an element that retains the unique properties of that element

atomic number

number of protons in the nucleus of an atom

compound

substance composed of two or more different elements joined by chemical bonds

electron

subatomic particle having a negative charge and nearly no mass; found orbiting the atom's nucleus

electron shell

area of space a given distance from an atom's nucleus in which electrons are grouped

element

substance that cannot be created or broken down by ordinary chemical means

isotope

one of the variations of an element in which the number of neutrons differ from each other

mass number

sum of the number of protons and neutrons in the nucleus of an atom

matter

physical substance; that which occupies space and has mass

neutron

heavy subatomic particle having no electrical charge and found in the atom's nucleus

periodic table of the elements

arrangement of the elements in a table according to their atomic number; elements having similar properties because of their electron arrangements compose columns in the table, while elements having the same number of valence shells compose rows in the table

proton

heavy subatomic particle having a positive charge and found in the atom's nucleus

radioactive isotope

unstable, heavy isotope that gives off subatomic particles, or electromagnetic energy, as it decays; also called radioisotopes

valence shell

outermost electron shell of an atom

OU Human Physiology: Chemical Bonds By the end of this section, you will be able to:

- Explain the relationship between molecules and compounds
- Distinguish between ions, cations, and anions
- Identify the key difference between ionic and covalent bonds
- Distinguish between nonpolar and polar covalent bonds
- Explain how water molecules link via hydrogen bonds

Atoms separated by a great distance cannot link; rather, they must come close enough for the electrons in their valence shells to interact. But do atoms ever actually touch one another? Most physicists would say no, because the negatively charged electrons in their valence shells repel one another. No force within the human body—or anywhere in the natural world—is strong enough to overcome this electrical repulsion. So when you read about atoms linking together or colliding, bear in mind that the atoms are not merging in a physical sense.

Instead, atoms link by forming a chemical bond. A **bond** is a weak or strong electrical attraction that holds atoms in the same vicinity. The new grouping is typically more stable—less likely to react again—than its component atoms were when they were separate. A more or less stable grouping of two or more atoms held together by chemical bonds is called a **molecule**. The bonded atoms may be of the same element, as in the case of H_2 , which is called molecular hydrogen or hydrogen gas. When a molecule is made up of two or more atoms of different elements, it is called a chemical **compound**. Thus, a unit of water, or H_2O , is a compound, as is a single molecule of the gas methane, or CH_4 .

Three types of chemical bonds are important in human physiology, because they hold together substances that are used by the body for critical aspects of homeostasis, signaling, and energy production, to name just a few important processes. These are ionic bonds, covalent bonds, and hydrogen bonds.

Ions and Ionic Bonds

Recall that an atom typically has the same number of positively charged protons and negatively charged electrons. As long as this situation remains, the atom is electrically neutral. But when an atom participates in a chemical reaction that results in the donation or acceptance of one or more electrons, the atom will then become positively or negatively charged. This happens frequently for most atoms in order to have a full valence shell, as described previously. This can happen either by gaining electrons to fill a shell that is more than half-full, or by giving away electrons to empty a shell than is less than half-full, thereby leaving the next smaller electron shell as the new, full, valence shell. An atom that has an electrical charge—whether positive or negative—is an **ion**.

Note:



Visit this <u>website</u> to learn about electrical energy and the attraction/repulsion of charges. What happens to the charged electroscope when a conductor is moved between its plastic sheets, and why?

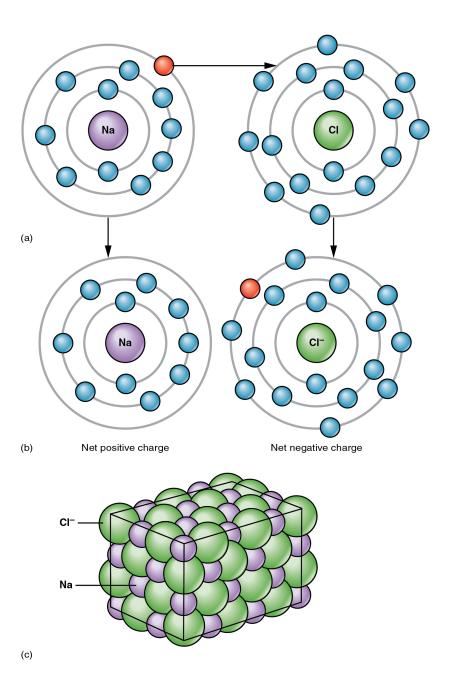
Potassium (K), for instance, is an important element in all body cells. Its atomic number is 19. It has just one electron in its valence shell. This characteristic makes potassium highly likely to participate in chemical reactions in which it donates one electron. (It is easier for potassium to donate one electron than to gain seven electrons.) The loss will cause the positive charge of potassium's protons to be more influential than the negative charge of potassium's electrons. In other words, the resulting potassium ion will be slightly positive. A potassium ion is written K⁺, indicating that it has lost a single electron. A positively charged ion is known as a **cation**.

Now consider fluorine (F), a component of bones and teeth. Its atomic number is nine, and it has seven electrons in its valence shell. Thus, it is highly likely to bond with other atoms in such a way that fluorine accepts one electron (it is easier for fluorine to gain one electron than to donate seven electrons). When it does, its electrons will outnumber its protons by one, and it will have an overall negative charge. The ionized form of fluorine is called fluoride, and is written as F⁻. A negatively charged ion is known as an **anion**.

Atoms that have more than one electron to donate or accept will end up with stronger positive or negative charges. A cation that has donated two electrons has a net charge of +2. Using magnesium (Mg) as an example, this can be written Mg^{++} or Mg^{2+} . An anion that has accepted two electrons has a net charge of -2. The ionic form of selenium (Se), for example, is typically written Se^{2-} .

The opposite charges of cations and anions exert a moderately strong mutual attraction that keeps the atoms in close proximity forming an ionic bond. An **ionic bond** is an ongoing, close association between ions of opposite charge. The table salt you sprinkle on your food owes its existence to ionic bonding. As shown in [link], sodium commonly donates an electron to chlorine, becoming the cation Na⁺. When chlorine accepts the electron, it becomes the chloride anion, Cl⁻. With their opposing charges, these two ions strongly attract each other.

Ionic Bonding



(a) Sodium readily donates the solitary electron in its valence shell to chlorine, which needs only one electron to have a full valence shell.

(b) The opposite electrical charges of the resulting sodium cation and chloride anion result in the formation of a bond of attraction called an ionic bond. (c) The attraction of

many sodium and chloride ions results in the formation of large groupings called crystals.

Water is an essential component of life because it is able to break the ionic bonds in salts to free the ions. In fact, in biological fluids, most individual atoms exist as ions. These dissolved ions produce electrical charges within the body. The behavior of these ions produces the tracings of heart and brain function observed as waves on an electrocardiogram (EKG or ECG) or an electroencephalogram (EEG). The electrical activity that derives from the interactions of the charged ions is why they are also called electrolytes.

Covalent Bonds

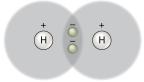
Unlike ionic bonds formed by the attraction between a cation's positive charge and an anion's negative charge, molecules formed by a **covalent bond** share electrons in a mutually stabilizing relationship. Like next-door neighbors whose kids hang out first at one home and then at the other, the atoms do not lose or gain electrons permanently. Instead, the electrons move back and forth between the elements. Because of the close sharing of pairs of electrons (one electron from each of two atoms), covalent bonds are stronger than ionic bonds.

Nonpolar Covalent Bonds

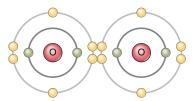
[link] shows several common types of covalent bonds. Notice that the two covalently bonded atoms typically share just one or two electron pairs, though larger sharings are possible. The important concept to take from this is that in covalent bonds, electrons in the outermost valence shell are shared to fill the valence shells of both atoms, ultimately stabilizing both of the atoms involved. In a single covalent bond, a single electron is shared between two atoms, while in a double covalent bond, two pairs of electrons are shared between two atoms. There even are triple covalent bonds, where three atoms are shared.

Covalent Bonding

(a) A single covalent bond: hydrogen gas (H—H). Two atoms of hydrogen each share their solitary electron in a single covalent bond.

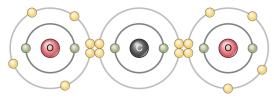


(b) A double covalent bond: oxygen gas (O=O). An atom of oxygen has six electrons in its valence shell; thus, two more would make it stable. Two atoms of oxygen achieve stability by sharing two pairs of electrons in a double covalent bond.



Molecule of oxygen gas (O₂)

(c) Two double covalent bonds: carbon dioxide (O=C=O). An atom of carbon has four electrons in its valence shell; thus, four more would make it stable. An atom of carbon and two atoms of oxygen achieve stability by sharing two electron pairs each, in two double covalent bonds.



You can see that the covalent bonds shown in [link] are balanced. The sharing of the negative electrons is relatively equal, as is the electrical pull of the positive protons in the nucleus of the atoms involved. This is why covalently bonded molecules that are electrically balanced in this way are described as nonpolar; that is, no region of the molecule is either more positive or more negative than any other.

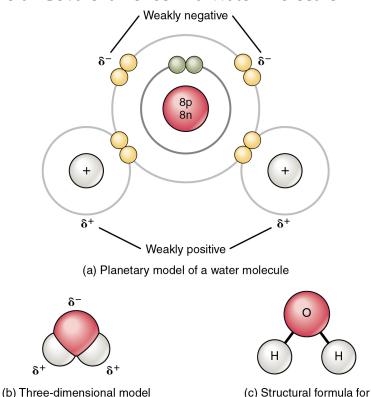
Polar Covalent Bonds

Groups of legislators with completely opposite views on a particular issue are often described as "polarized" by news writers. In chemistry, a **polar molecule** is a molecule that contains regions that have opposite electrical charges. Polar molecules occur when atoms share electrons unequally, in polar covalent bonds.

The most familiar example of a polar molecule is water ([link]). The molecule has three parts: one atom of oxygen, the nucleus of which

contains eight protons, and two hydrogen atoms, whose nuclei each contain only one proton. Because every proton exerts an identical positive charge, a nucleus that contains eight protons exerts a charge eight times greater than a nucleus that contains one proton. This means that the negatively charged electrons present in the water molecule are more strongly attracted to the oxygen nucleus than to the hydrogen nuclei. Each hydrogen atom's single negative electron therefore migrates toward the oxygen atom, making the oxygen end of their bond slightly more negative than the hydrogen end of their bond.

Polar Covalent Bonds in a Water Molecule



of a water molecule

What is true for the bonds is true for the water molecule as a whole; that is, the oxygen region has a slightly negative charge and the regions of the hydrogen atoms have a slightly positive charge. These charges are often referred to as "partial charges" because the strength of the charge is less than one full electron, as would occur in an ionic bond. As shown in [link], regions of weak polarity are indicated with the Greek letter delta (∂) and a plus (+) or minus (–) sign.

water molecule

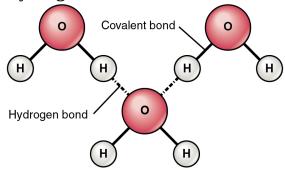
Even though a single water molecule is unimaginably tiny, it has mass, and the opposing electrical charges on the molecule pull that mass in such a way that it creates a shape somewhat like a triangular tent (see [link]b). This dipole, with the positive charges at one end formed by the hydrogen atoms at the "bottom" of the tent and the negative charge at the opposite end (the oxygen atom at the "top" of the tent) makes the charged regions highly likely to interact with charged regions of other polar molecules. For human physiology, the resulting bond is one of the most important formed by water—the hydrogen bond.

Hydrogen Bonds

A **hydrogen bond** is formed when a weakly positive hydrogen atom already bonded to one electronegative atom (for example, the oxygen in the water molecule) is attracted to another electronegative atom from another molecule. In other words, hydrogen bonds always include hydrogen that is already part of a polar molecule.

The most common example of hydrogen bonding in the natural world occurs between molecules of water. It happens before your eyes whenever two raindrops merge into a larger bead, or a creek spills into a river. Hydrogen bonding occurs because the weakly negative oxygen atom in one water molecule is attracted to the weakly positive hydrogen atoms of two other water molecules ([link]).

Hydrogen Bonds between Water Molecules



Notice that the bonds occur between the weakly positive charge on the hydrogen atoms and the weakly negative charge on the oxygen atoms. Hydrogen bonds are relatively weak, and therefore are indicated with a dotted (rather than a solid) line.

Water molecules also strongly attract other types of charged molecules as well as ions. This explains why "table salt," for example, actually is a molecule called a "salt" in chemistry, which consists of equal numbers of positively-charged sodium (Na⁺) and negatively-charged chloride (Cl⁻), dissolves so readily in water, in this case forming dipole-ion bonds between the water and the electrically-charged ions (electrolytes). Water molecules also repel molecules with nonpolar covalent bonds, like fats, lipids, and oils. You can demonstrate this with a simple kitchen experiment: pour a teaspoon of vegetable oil, a compound formed by nonpolar covalent bonds, into a glass of water. Instead of instantly dissolving in the water, the oil forms a distinct bead because the polar water molecules repel the nonpolar oil.

Chapter Review

Each moment of life, atoms of oxygen, carbon, hydrogen, and the other elements of the human body are making and breaking chemical bonds. Ions are charged atoms that form when an atom donates or accepts one or more negatively charged electrons. Cations (ions with a positive charge) are attracted to anions (ions with a negative charge). This attraction is called an ionic bond. In covalent bonds, the participating atoms do not lose or gain electrons, but rather share them. Molecules with nonpolar covalent bonds are electrically balanced, and have a linear three-dimensional shape. Molecules with polar covalent bonds have "poles"—regions of weakly positive and negative charge—and have a triangular three-dimensional shape. An atom of oxygen and two atoms of hydrogen form water molecules by means of polar covalent bonds. Hydrogen bonds link

hydrogen atoms already participating in polar covalent bonds to anions or electronegative regions of other polar molecules. Hydrogen bonds link water molecules, resulting in the properties of water that are important to living things.

Glossary

anion

atom with a negative charge

bond

electrical force linking atoms

cation

atom with a positive charge

covalent bond

chemical bond in which two atoms share electrons, thereby completing their valence shells

hydrogen bond

dipole-dipole bond in which a hydrogen atom covalently bonded to an electronegative atom is weakly attracted to a second electronegative atom

ion

atom with an overall positive or negative charge

ionic bond

attraction between an anion and a cation

molecule

two or more atoms covalently bonded together

polar molecule

molecule with regions that have opposite charges resulting from uneven numbers of electrons in the nuclei of the atoms participating in the covalent bond

OU Human Physiology: Chemical Reactions By the end of this section, you will be able to:

- Distinguish between kinetic and potential energy, and between exergonic and endergonic chemical reactions
- Identify four forms of energy important in human functioning
- Describe the three basic types of chemical reactions
- Identify several factors influencing the rate of chemical reactions

One characteristic of a living organism is metabolism, which is the sum total of all of the chemical reactions that go on to maintain that organism's health and life. The bonding processes you have learned thus far are anabolic chemical reactions; that is, they form larger molecules from smaller molecules or atoms. But recall that metabolism can proceed in another direction: in catabolic chemical reactions, bonds between components of larger molecules break, releasing smaller molecules or atoms. Both types of reaction involve exchanges not only of matter, but of energy.

The Role of Energy in Chemical Reactions

Chemical reactions require a sufficient amount of energy to cause the matter to collide with enough precision and force that old chemical bonds can be broken and new ones formed. In general, **kinetic energy** is the form of energy powering any type of matter in motion. Imagine you are building a brick wall. The energy it takes to lift and place one brick atop another is kinetic energy—the energy matter possesses because of its motion. Once the wall is in place, it stores potential energy. **Potential energy** is the energy of position, or the energy matter possesses because of the positioning or structure of its components. If the brick wall collapses, the stored potential energy is released as kinetic energy as the bricks fall.

In the human body, potential energy is stored in the bonds between atoms and molecules. **Chemical energy** is the form of potential energy in which energy is stored in chemical bonds. When those bonds are formed, chemical energy is invested, and when they break, chemical energy is released. Notice that chemical energy, like all energy, is neither created nor

destroyed; rather, it is converted from one form to another. When you eat an energy bar before heading out the door for a hike, the honey, nuts, and other foods the bar contains are broken down and rearranged by your body into molecules that your muscle cells convert to kinetic energy.

Chemical reactions that release more energy than they absorb are characterized as exergonic. The catabolism of the foods in your energy bar is an example. Some of the chemical energy stored in the bar is absorbed into molecules your body uses for fuel, but some of it is released—for example, as heat. In contrast, chemical reactions that absorb more energy than they release are endergonic. These reactions require energy input, and the resulting molecule stores not only the chemical energy in the original components, but also the energy that fueled the reaction. Because energy is neither created nor destroyed, where does the energy needed for endergonic reactions come from? In many cases, it comes from exergonic reactions.

Forms of Energy Important in Human Functioning

You have already learned that chemical energy is absorbed, stored, and released by chemical bonds. In addition to chemical energy, mechanical, radiant, and electrical energy are important in human functioning.

- Mechanical energy, which is stored in physical systems such as machines, engines, or the human body, directly powers the movement of matter. When you lift a brick into place on a wall, your muscles provide the mechanical energy that moves the brick.
- Radiant energy is energy emitted and transmitted as waves rather than matter. These waves vary in length from long radio waves and microwaves to short gamma waves emitted from decaying atomic nuclei. The full spectrum of radiant energy is referred to as the electromagnetic spectrum. The body uses the ultraviolet energy of sunlight to convert a compound in skin cells to vitamin D, which is essential to human functioning. The human eye evolved to see the wavelengths that comprise the colors of the rainbow, from red to violet, so that range in the spectrum is called "visible light."
- Electrical energy, supplied by electrolytes in cells and body fluids, contributes to the voltage changes that help transmit impulses in nerve

and muscle cells.

Characteristics of Chemical Reactions

All chemical reactions begin with a **reactant**, the general term for the one or more substances that enter into the reaction. Sodium and chloride ions, for example, are the reactants in the production of table salt. The one or more substances produced by a chemical reaction are called the **product**.

In chemical reactions, the components of the reactants—the elements involved and the number of atoms of each—are all present in the product(s). Similarly, there is nothing present in the products that are not present in the reactants. This is because chemical reactions are governed by the law of conservation of mass, which states that matter cannot be created or destroyed in a chemical reaction.

Just as you can express mathematical calculations in equations such as 2 + 7 = 9, you can use chemical equations to show how reactants become products. As in math, chemical equations proceed from left to right, but instead of an equal sign, they employ an arrow or arrows indicating the direction in which the chemical reaction proceeds. For example, the chemical reaction in which one atom of nitrogen and three atoms of hydrogen produce ammonia would be written as $N+3H \rightarrow NH_3$. Correspondingly, the breakdown of ammonia into its components would be written as $NH_3 \rightarrow N+3H$.

Notice that, in the first example, a nitrogen (N) atom and three hydrogen (H) atoms bond to form a compound. This anabolic reaction requires energy, which is then stored within the compound's bonds. Such reactions are referred to as synthesis reactions. A **synthesis reaction** is a chemical reaction that results in the synthesis (joining) of components that were formerly separate ([link]a). Again, nitrogen and hydrogen are reactants in a synthesis reaction that yields ammonia as the product. The general equation for a synthesis reaction is $A + B \rightarrow AB$.

The Three Fundamental Chemical Reactions

 a) In a synthesis reaction, two components bond to make a larger molecule. Energy is required and is stored in the bond:

b) In a decomposition reaction, bonds between components of a larger molecule are broken, resulting in smaller products:

c) In an exchange reaction, bonds are both formed and broken such that the components of the reactants are rearranged:

The atoms and molecules involved in the three fundamental chemical reactions can be imagined as words.

In the second example, ammonia is catabolized into its smaller components, and the potential energy that had been stored in its bonds is released. Such reactions are referred to as decomposition reactions. A **decomposition** reaction is a chemical reaction that breaks down or "de-composes" something larger into its constituent parts (see [link]b). The general equation for a decomposition reaction is: $AB \rightarrow A + B$.

An **exchange reaction** is a chemical reaction in which both synthesis and decomposition occur, chemical bonds are both formed and broken, and chemical energy is absorbed, stored, and released (see [link]c). The simplest form of an exchange reaction might be: $A + BC \rightarrow AB + C$. Notice that, to produce these products, B and C had to break apart in a decomposition reaction, whereas A and B had to bond in a synthesis reaction. A more complex exchange reaction might be: $AB + CD \rightarrow AC + BD$. Another example might be: $AB + CD \rightarrow AD + BC$.

In theory, any chemical reaction can proceed in either direction under the right conditions. Reactants may synthesize into a product that is later decomposed. Reversibility is also a quality of exchange reactions. For instance, $A + BC \rightarrow AB + C$ could then reverse to $AB + C \rightarrow A + BC$. This reversibility of a chemical reaction is indicated with a double arrow: $A + BC \rightleftharpoons AB + C$. Still, in the human body, many chemical reactions do

proceed in a predictable direction, either one way or the other. You can think of this more predictable path as the path of least resistance because, typically, the alternate direction requires more energy.

Factors Influencing the Rate of Chemical Reactions

If you pour vinegar into baking soda, the reaction is instantaneous; the concoction will bubble and fizz. But many chemical reactions take time. A variety of factors influence the rate of chemical reactions. This section, however, will consider only the most important in human functioning.

Properties of the Reactants

If chemical reactions are to occur quickly, the atoms in the reactants have to have easy access to one another. Thus, the greater the surface area of the reactants, the more readily they will interact. When you pop a cube of cheese into your mouth, you chew it before you swallow it. Among other things, chewing increases the surface area of the food so that digestive chemicals can more easily get at it. As a general rule, gases tend to react faster than liquids or solids, again because it takes energy to separate particles of a substance, and gases by definition already have space between their particles. Similarly, the larger the molecule, the greater the number of total bonds, so reactions involving smaller molecules, with fewer total bonds, would be expected to proceed faster.

In addition, recall that some elements are more reactive than others. Reactions that involve highly reactive elements like hydrogen proceed more quickly than reactions that involve less reactive elements. Reactions involving stable elements like helium are not likely to happen at all.

Temperature

Nearly all chemical reactions occur at a faster rate at higher temperatures. Recall that kinetic energy is the energy of matter in motion. The kinetic energy of subatomic particles increases in response to increases in thermal energy. The higher the temperature, the faster the particles move, and the more likely they are to come in contact and react.

Concentration and Pressure

If just a few people are dancing at a club, they are unlikely to step on each other's toes. But as more and more people get up to dance—especially if the music is fast—collisions are likely to occur. It is the same with chemical reactions: the more particles present within a given space, the more likely those particles are to bump into one another. This means that chemists can speed up chemical reactions not only by increasing the **concentration** of particles—the number of particles in the space—but also by decreasing the volume of the space, which would correspondingly increase the pressure. If there were 100 dancers in that club, and the manager abruptly moved the party to a room half the size, the concentration of the dancers would double in the new space, and the likelihood of collisions would increase accordingly.

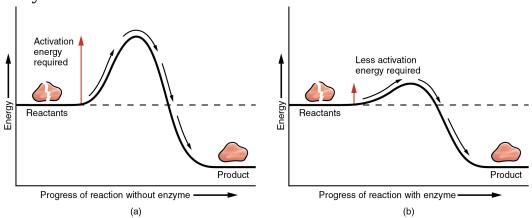
Enzymes and Other Catalysts

For two chemicals in nature to react with each other they first have to come into contact, and this occurs through random collisions. Because heat helps increase the kinetic energy of atoms, ions, and molecules, it promotes their collision. But in the body, extremely high heat—such as a very high fever—can damage body cells and be life-threatening. On the other hand, normal body temperature is not high enough to promote the chemical reactions that sustain life. That is where catalysts come in.

In chemistry, a **catalyst** is a substance that increases the rate of a chemical reaction without itself undergoing any change. You can think of a catalyst as a chemical change agent. They help increase the rate and force at which atoms, ions, and molecules collide, thereby increasing the probability that their valence shell electrons will interact.

The most important catalysts in the human body are enzymes. An **enzyme** is a catalyst composed of protein or ribonucleic acid (RNA), both of which will be discussed later in this chapter. Like all catalysts, enzymes work by lowering the level of energy that needs to be invested in a chemical reaction. A chemical reaction's **activation energy** is the "threshold" level of energy needed to break the bonds in the reactants. Once those bonds are broken, new arrangements can form. Without an enzyme to act as a catalyst, a much larger investment of energy is needed to ignite a chemical reaction ([link]).

Enzymes



Enzymes decrease the activation energy required for a given chemical reaction to occur. (a) Without an enzyme, the energy input needed for a reaction to begin is high. (b) With the help of an enzyme, less energy is needed for a reaction to begin.

Enzymes are critical to the body's healthy functioning. They assist, for example, with the breakdown of food and its conversion to energy. In fact, most of the chemical reactions in the body are facilitated by enzymes.

Chapter Review

Chemical reactions, in which chemical bonds are broken and formed, require an initial investment of energy. Kinetic energy, the energy of matter

in motion, fuels the collisions of atoms, ions, and molecules that are necessary if their old bonds are to break and new ones to form. All molecules store potential energy, which is released when their bonds are broken.

Four forms of energy essential to human functioning are: chemical energy, which is stored and released as chemical bonds are formed and broken; mechanical energy, which directly powers physical activity; radiant energy, emitted as waves such as in sunlight; and electrical energy, the power of moving electrons.

Chemical reactions begin with reactants and end with products. Synthesis reactions bond reactants together, a process that requires energy, whereas decomposition reactions break the bonds within a reactant and thereby release energy. In exchange reactions, bonds are both broken and formed, and energy is exchanged.

The rate at which chemical reactions occur is influenced by several properties of the reactants: temperature, concentration and pressure, and the presence or absence of a catalyst. An enzyme is a catalytic protein that speeds up chemical reactions in the human body.

Glossary

activation energy

amount of energy greater than the energy contained in the reactants, which must be overcome for a reaction to proceed

catalyst

substance that increases the rate of a chemical reaction without itself being changed in the process

chemical energy

form of energy that is absorbed as chemical bonds form, stored as they are maintained, and released as they are broken

concentration

number of particles within a given space

decomposition reaction

type of catabolic reaction in which one or more bonds within a larger molecule are broken, resulting in the release of smaller molecules or atoms

enzyme

protein or RNA that catalyzes chemical reactions

exchange reaction

type of chemical reaction in which bonds are both formed and broken, resulting in the transfer of components

kinetic energy

energy that matter possesses because of its motion

potential energy

stored energy matter possesses because of the positioning or structure of its components

product

one or more substances produced by a chemical reaction

reactant

one or more substances that enter into the reaction

synthesis reaction

type of anabolic reaction in which two or more atoms or molecules bond, resulting in the formation of a larger molecule OU Human Physiology: Inorganic Compounds Essential to Human Functioning

By the end of this section, you will be able to:

- Compare and contrast inorganic and organic compounds
- Identify the properties of water that make it essential to life
- Explain the role of salts in body functioning
- Distinguish between acids and bases, and explain their role in pH
- Discuss the role of buffers in helping the body maintain pH homeostasis

The concepts you have learned so far in this chapter govern all forms of matter, and would work as a foundation for geology as well as biology. This section of the chapter narrows the focus to the chemistry of human life; that is, the compounds important for the body's structure and function. In general, these compounds are either inorganic or organic.

- An **inorganic compound** is a substance that does not contain both carbon and hydrogen. A great many inorganic compounds do contain hydrogen atoms, such as water (H₂O) and the hydrochloric acid (HCl) produced by your stomach. In contrast, only a handful of inorganic compounds contain carbon atoms. Carbon dioxide (CO₂) is one of the few examples.
- An **organic compound**, then, is a substance that contains both carbon and hydrogen. Organic compounds are synthesized via covalent bonds within living organisms, including the human body. Recall that carbon and hydrogen are the second and third most abundant elements in your body. You will soon discover how these two elements combine in the foods you eat, in the compounds that make up your body structure, and in the chemicals that fuel your functioning.

The following section examines the three groups of inorganic compounds essential to life: water, salts, acids, and bases. Organic compounds are covered later in the chapter.

Water

As much as 70 percent of an adult's body weight is water. This water is contained both within the cells and between the cells that make up tissues and organs. Its several roles make water indispensable to human functioning.

Water as a Lubricant and Cushion

Water is a major component of many of the body's lubricating fluids. Just as oil lubricates the hinge on a door, water in synovial fluid lubricates the actions of body joints, and water in pleural fluid helps the lungs expand and recoil with breathing. Watery fluids help keep food flowing through the digestive tract, and ensure that the movement of adjacent abdominal organs is friction free.

Water also protects cells and organs from physical trauma, cushioning the brain within the skull, for example, and protecting the delicate nerve tissue of the eyes. Water cushions a developing fetus in the mother's womb as well.

Water as a Heat Sink

A heat sink is a substance or object that absorbs and dissipates heat but does not experience a corresponding increase in temperature. In the body, water absorbs the heat generated by chemical reactions without greatly increasing in temperature. Moreover, when the environmental temperature soars, the water stored in the body helps keep the body cool. This cooling effect happens as warm blood from the body's core flows to the blood vessels just under the skin and is transferred to the environment. At the same time, sweat glands release warm water in sweat. As the water evaporates into the air, it carries away heat, and then the cooler blood from the periphery circulates back to the body core.

Water as a Component of Liquid Mixtures

A mixture is a combination of two or more substances, each of which maintains its own chemical identity. In other words, the constituent substances are not chemically bonded into a new, larger chemical compound. The concept is easy to imagine if you think of powdery substances such as flour and sugar; when you stir them together in a bowl, they obviously do not bond to form a new compound. The room air you breathe is a gaseous mixture, containing three discrete elements—nitrogen, oxygen, and argon—and one compound, carbon dioxide. There are three types of liquid mixtures, all of which contain water as a key component. These are solutions, colloids, and suspensions.

For cells in the body to survive, they must be kept moist in a water-based liquid called a solution. In chemistry, a liquid **solution** consists of a solvent that dissolves a substance called a solute. An important characteristic of solutions is that they are homogeneous; that is, the solute molecules are distributed evenly throughout the solution. If you were to stir a teaspoon of sugar into a glass of water, the sugar would dissolve into sugar molecules separated by water molecules. The ratio of sugar to water in the left side of the glass would be the same as the ratio of sugar to water in the right side of the glass. If you were to add more sugar, the ratio of sugar to water would change, but the distribution—provided you had stirred well—would still be even.

Water is considered the "universal solvent" and it is believed that life cannot exist without water because of this. Water is certainly the most abundant solvent in the body; essentially all of the body's chemical reactions occur among compounds dissolved in water. Because water molecules are polar, with regions of positive and negative electrical charge, water readily dissolves ionic compounds and polar covalent compounds. Such compounds are referred to as hydrophilic, or "water-loving." As mentioned above, sugar dissolves well in water. This is because sugar molecules contain regions of hydrogen-oxygen polar bonds, making it hydrophilic. Nonpolar molecules, which do not readily dissolve in water, are called hydrophobic, or "water-fearing."

Concentrations of Solutes

Various mixtures of solutes and water are described in chemistry. The concentration of a given solute is the number of particles of that solute in a given space (oxygen makes up about 21 percent of atmospheric air). In the bloodstream of humans, glucose concentration is usually measured in milligram (mg) per deciliter (dL), and in a healthy adult averages about 100 mg/dL. Another method of measuring the concentration of a solute is by its molarilty—which is moles (M) of the molecules per liter (L). The mole of an element is its atomic weight, while a mole of a compound is the sum of the atomic weights of its components, called the molecular weight. An often-used example is calculating a mole of glucose, with the chemical formula $C_6H_{12}O_6$. Using the periodic table, the atomic weight of carbon (C) is 12.011 grams (g), and there are six carbons in glucose, for a total atomic weight of 72.066 g. Doing the same calculations for hydrogen (H) and oxygen (O), the molecular weight equals 180.156g (the "gram molecular weight" of glucose). When water is added to make one liter of solution, you have one mole (1M) of glucose. This is particularly useful in chemistry because of the relationship of moles to "Avogadro's number." A mole of any solution has the same number of particles in it: 6.02×10^{23} . Many substances in the bloodstream and other tissue of the body are measured in thousandths of a mole, or millimoles (mM).

A **colloid** is a mixture that is somewhat like a heavy solution. The solute particles consist of tiny clumps of molecules large enough to make the liquid mixture opaque (because the particles are large enough to scatter light). Familiar examples of colloids are milk and cream. In the thyroid glands, the thyroid hormone is stored as a thick protein mixture also called a colloid.

A **suspension** is a liquid mixture in which a heavier substance is suspended temporarily in a liquid, but over time, settles out. This separation of particles from a suspension is called sedimentation. An example of sedimentation occurs in the blood test that establishes sedimentation rate, or sed rate. The test measures how quickly red blood cells in a test tube settle out of the watery portion of blood (known as plasma) over a set period of time. Rapid sedimentation of blood cells does not normally happen in the healthy body, but aspects of certain diseases can cause blood cells to clump

together, and these heavy clumps of blood cells settle to the bottom of the test tube more quickly than do normal blood cells.

The Role of Water in Chemical Reactions

Two types of chemical reactions involve the creation or the consumption of water: dehydration synthesis and hydrolysis.

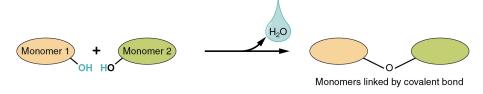
- In dehydration synthesis, one reactant gives up an atom of hydrogen and another reactant gives up a hydroxyl group (OH) in the synthesis of a new product. In the formation of their covalent bond, a molecule of water is released as a byproduct ([link]). This is also sometimes referred to as a condensation reaction.
- In hydrolysis, a molecule of water disrupts a compound, breaking its bonds. The water is itself split into H and OH. One portion of the severed compound then bonds with the hydrogen atom, and the other portion bonds with the hydroxyl group.

These reactions are reversible, and play an important role in the chemistry of organic compounds (which will be discussed shortly).

Dehydration Synthesis and Hydrolysis

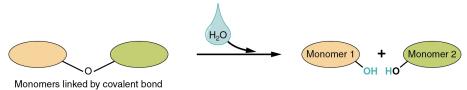
(a) Dehydration synthesis

Monomers are joined by removal of OH from one monomer and removal of H from the other at the site of bond formation.



(b) Hydrolysis

Monomers are released by the addition of a water molecule, adding OH to one monomer and H to the other.



Monomers, the basic units for building larger molecules, form polymers (two or more chemically-bonded

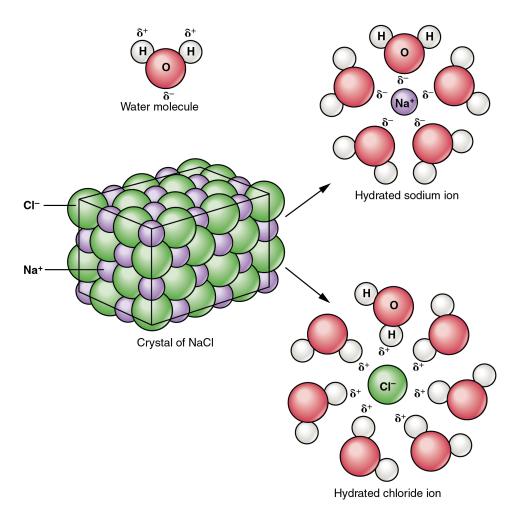
monomers). (a) In dehydration synthesis, two monomers are covalently bonded in a reaction in which one gives up a hydroxyl group and the other a hydrogen atom. A molecule of water is released as a byproduct during dehydration reactions. (b) In hydrolysis, the covalent bond between two monomers is split by the addition of a hydrogen atom to one and a hydroxyl group to the other, which requires the contribution of one molecule of water.

Salts

Recall that salts are formed when ions form ionic bonds. In these reactions, one atom gives up one or more electrons, and thus becomes positively charged, whereas the other accepts one or more electrons and becomes negatively charged. You can now define a salt as a substance that, when dissolved in water, dissociates into ions other than H⁺ or OH⁻. This fact is important in distinguishing salts from acids and bases, discussed next.

A typical salt, NaCl, dissociates completely in water ([link]). The positive and negative regions on the water molecule (the hydrogen and oxygen ends respectively) attract the negative chloride and positive sodium ions, pulling them away from each other. Again, whereas nonpolar and polar covalently bonded compounds break apart into molecules in solution, salts dissociate into ions. These ions are electrolytes; they are capable of conducting an electrical current in solution. This property is critical to the function of ions in transmitting nerve impulses and prompting muscle contraction.

Dissociation of Sodium Chloride in Water



Notice that the crystals of sodium chloride dissociate not into molecules of NaCl, but into Na⁺ cations and Cl⁻ anions, each completely surrounded by water molecules.

Many other salts are important in the body. For example, bile salts produced by the liver help break apart dietary fats, and calcium phosphate salts form the mineral portion of teeth and bones.

Acids and Bases

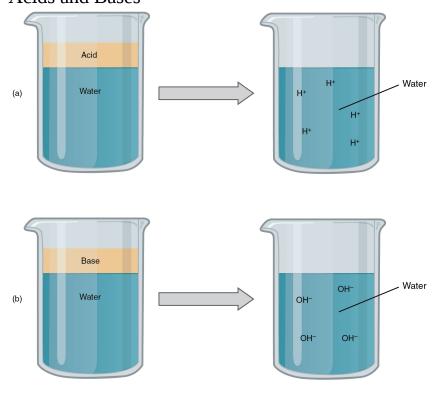
Acids and bases, like salts, dissociate in water into electrolytes. Acids and bases can very much change the properties of the solutions in which they

are dissolved.

Acids

An **acid** is a substance that releases hydrogen ions (H⁺) in solution ([link]a). Because an atom of hydrogen has just one proton and one electron, a positively charged hydrogen ion is simply a proton. This solitary proton is highly likely to participate in chemical reactions. Strong acids are compounds that release all of their H⁺ in solution; that is, they ionize completely. Hydrochloric acid (HCl), which is released from cells in the lining of the stomach, is a strong acid because it releases all of its H⁺ in the stomach's watery environment. This strong acid aids in digestion and kills ingested microbes. Weak acids do not ionize completely; that is, some of their hydrogen ions remain bonded within a compound in solution. An example of a weak acid is vinegar, or acetic acid; it is called acetate after it gives up a proton.

Acids and Bases



(a) In aqueous solution, an acid dissociates into

hydrogen ions (H⁺) and anions. Nearly every molecule of a strong acid dissociates, producing a high concentration of H⁺. (b) In aqueous solution, a base dissociates into hydroxyl ions (OH⁻) and cations. Nearly every molecule of a strong base dissociates, producing a high concentration of OH⁻.

Bases

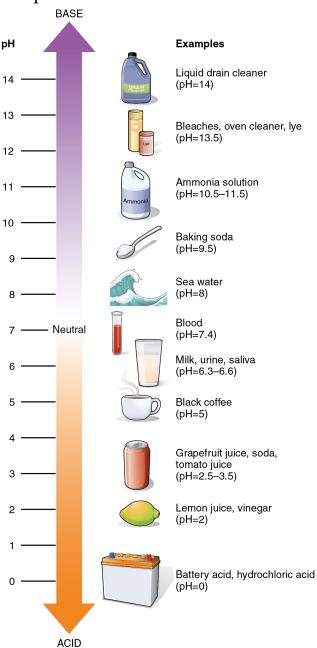
A **base** is a substance that releases hydroxyl ions (OH⁻) in solution, or one that accepts H⁺ already present in solution (see [link]b). The hydroxyl ions or other base combine with H⁺ present to form a water molecule, thereby removing H⁺ and reducing the solution's acidity. Strong bases release most or all of their hydroxyl ions; weak bases release only some hydroxyl ions or absorb only a few H⁺. Food mixed with hydrochloric acid from the stomach would burn the small intestine, the next portion of the digestive tract after the stomach, if it were not for the release of bicarbonate (HCO₃⁻), a weak base that attracts H⁺. Bicarbonate accepts some of the H⁺ protons, thereby reducing the acidity of the solution.

The Concept of pH

The relative acidity or alkalinity of a solution can be indicated by its pH. A solution's **pH** is the negative, base-10 logarithm of the hydrogen ion (H⁺) concentration of the solution. As an example, a pH 4 solution has an H⁺ concentration that is ten times greater than that of a pH 5 solution. That is, a solution with a pH of 4 is ten times more acidic than a solution with a pH of 5. The concept of pH will begin to make more sense when you study the pH scale, like that shown in [link]. The scale consists of a series of increments ranging from 0 to 14. A solution with a pH of 7 is considered neutral—neither acidic nor basic. Pure water has a pH of 7. The lower the number

below 7, the more acidic the solution, or the greater the concentration of H^+ . The concentration of hydrogen ions at each pH value is 10 times different than the next pH. For instance, a pH value of 4 corresponds to a proton concentration of 10^{-4} M, or 0.0001M, while a pH value of 5 corresponds to a proton concentration of 10^{-5} M, or 0.00001M. The higher the number above 7, the more basic (alkaline) the solution, or the lower the concentration of H^+ . Human urine, for example, is ten times more acidic than pure water, and HCl is 10,000,000 times more acidic than water.

The pH Scale



Buffers

The pH of human blood normally ranges from 7.35 to 7.45, although it is typically identified as pH 7.4. At this slightly basic pH, blood can reduce the acidity resulting from the carbon dioxide (CO₂) constantly being released into the bloodstream by the trillions of cells in the body. Homeostatic mechanisms (along with exhaling CO₂ while breathing) normally keep the pH of blood within this narrow range. This is critical, because fluctuations—either too acidic or too alkaline—can lead to lifethreatening disorders.

All cells of the body depend on homeostatic regulation of acid—base balance at a pH of approximately 7.4. The body therefore has several mechanisms for this regulation, involving breathing, the excretion of chemicals in urine, and the internal release of chemicals collectively called buffers into body fluids. A **buffer** is a solution of a weak acid and its conjugate base. A buffer can neutralize small amounts of acids or bases in body fluids. For example, if there is even a slight decrease below 7.35 in the pH of a bodily fluid, the buffer in the fluid—in this case, acting as a weak base—will bind the excess hydrogen ions. In contrast, if pH rises above 7.45, the buffer will act as a weak acid and contribute hydrogen ions.

Note:

Homeostatic Imbalances

Acids and Bases

Excessive acidity of the blood and other body fluids is known as acidosis. Common causes of acidosis are situations and disorders that reduce the effectiveness of breathing, especially the person's ability to exhale fully, which causes a buildup of CO_2 (and H^+) in the bloodstream. Acidosis can also be caused by metabolic problems that reduce the level or function of buffers that act as bases, or that promote the production of acids. For instance, with severe diarrhea, too much bicarbonate can be lost from the body, allowing acids to build up in body fluids. In people with poorly managed diabetes (ineffective regulation of blood sugar), acids called ketones are produced as a form of body fuel. These can build up in the blood, causing a serious condition called diabetic ketoacidosis. Kidney

failure, liver failure, heart failure, cancer, and other disorders also can prompt metabolic acidosis.

In contrast, alkalosis is a condition in which the blood and other body fluids are too alkaline (basic). As with acidosis, respiratory disorders are a major cause; however, in respiratory alkalosis, carbon dioxide levels fall too low. Lung disease, aspirin overdose, shock, and ordinary anxiety can cause respiratory alkalosis, which reduces the normal concentration of H⁺. Metabolic alkalosis often results from prolonged, severe vomiting, which causes a loss of hydrogen and chloride ions (as components of HCl). Medications also can prompt alkalosis. These include diuretics that cause the body to lose potassium ions, as well as antacids when taken in excessive amounts, for instance by someone with persistent heartburn or an ulcer.

Chapter Review

Inorganic compounds essential to human functioning include water, salts, acids, and bases. These compounds are inorganic; that is, they do not contain both hydrogen and carbon. Water is a lubricant and cushion, a heat sink, a component of liquid mixtures, a byproduct of dehydration synthesis reactions, and a reactant in hydrolysis reactions. Salts are compounds that, when dissolved in water, dissociate into ions other than H⁺ or OH⁻. In contrast, acids release H⁺ in solution, making it more acidic. Bases accept H⁺, thereby making the solution more alkaline (caustic).

The pH of any solution is its relative concentration of H⁺. A solution with pH 7 is neutral. Solutions with pH below 7 are acids, and solutions with pH above 7 are bases. A change in a single digit on the pH scale (e.g., from 7 to 8) represents a ten-fold increase or decrease in the concentration of H⁺. In a healthy adult, the pH of blood ranges from 7.35 to 7.45. Homeostatic control mechanisms important for keeping blood in a healthy pH range include chemicals called buffers, weak acids and weak bases released when the pH of blood or other body fluids fluctuates in either direction outside of this normal range.

Glossary

acid

compound that releases hydrogen ions (H⁺) in solution

base

compound that accepts hydrogen ions (H⁺) in solution

buffer

solution containing a weak acid or a weak base that opposes wide fluctuations in the pH of body fluids

colloid

liquid mixture in which the solute particles consist of clumps of molecules large enough to scatter light

inorganic compound

substance that does not contain both carbon and hydrogen

organic compound

substance that contains both carbon and hydrogen

pН

negative logarithm of the hydrogen ion (H⁺) concentration of a solution

solution

homogeneous liquid mixture in which a solute is dissolved into molecules within a solvent

suspension

liquid mixture in which particles distributed in the liquid settle out over time

OU Human Physiology: Organic Compounds Essential to Human Functioning

By the end of this section, you will be able to:

- Identify four types of organic molecules essential to human functioning
- Explain the chemistry behind carbon's affinity for covalently bonding in organic compounds
- Provide examples of three types of carbohydrates, and identify the primary functions of carbohydrates in the body
- Discuss four types of lipids important in human functioning
- Describe the structure of proteins, and discuss their importance to human functioning
- Identify the building blocks of nucleic acids, and the roles of DNA, RNA, and ATP in human functioning

Organic compounds typically consist of groups of carbon atoms covalently bonded to hydrogen, usually oxygen, and often other elements as well. Created by living things, they are found throughout the world, in soils and seas, commercial products, and every cell of the human body. The four types most important to human structure and function are carbohydrates, lipids, proteins, and nucleotides. Before exploring these compounds, you need to first understand the chemistry of carbon.

The Chemistry of Carbon

What makes organic compounds ubiquitous is the chemistry of their carbon core. Recall that carbon atoms have four electrons in their valence shell, and that the octet rule dictates that atoms tend to react in such a way as to complete their valence shell with eight electrons. Carbon atoms do not complete their valence shells by donating or accepting four electrons. Instead, they readily share electrons via covalent bonds.

Commonly, carbon atoms share with other carbon atoms, often forming a long carbon chain referred to as a carbon skeleton. When they do share, however, they do not share all their electrons exclusively with each other. Rather, carbon atoms tend to share electrons with a variety of other

elements, one of which is always hydrogen. Carbon and hydrogen groupings are called hydrocarbons. If you study the figures of organic compounds in the remainder of this chapter, you will see several with chains of hydrocarbons in one region of the compound.

Many combinations are possible to fill carbon's four "vacancies." Carbon may share electrons with oxygen or nitrogen or other atoms in a particular region of an organic compound. Moreover, the atoms to which carbon atoms bond may also be part of a functional group. A **functional group** is a group of atoms linked by strong covalent bonds and tending to function in chemical reactions as a single unit. You can think of functional groups as tightly knit "cliques" whose members are unlikely to be parted. Five functional groups are important in human physiology; these are the hydroxyl, carboxyl, amino, methyl and phosphate groups ([link]).

Functional Groups Important in Human Physiology		
Functional group	Structural formula	Importance
Hydroxyl	—О—Н	Hydroxyl groups are polar. They are components of all four types of organic compounds discussed in this chapter. They are involved in dehydration synthesis and hydrolysis reactions.
Carboxyl	O—C— OH	Carboxyl groups are found within fatty acids, amino acids, and many other acids.

Functional Groups Important in Human Physiology		
Functional group	Structural formula	Importance
Amino	—N—H ₂	Amino groups are found within amino acids, the building blocks of proteins.
Methyl	—C—H ₃	Methyl groups are found within amino acids.
Phosphate	—P—O ₄ ²⁻	Phosphate groups are found within phospholipids and nucleotides.

Carbon's affinity for covalent bonding means that many distinct and relatively stable organic molecules nevertheless readily form larger, more complex molecules. Any large molecule is referred to as **macromolecule** (macro-= "large"), and the organic compounds in this section all fit this description. However, some macromolecules are made up of several "copies" of single units called monomer (mono-= "one"; -mer = "part"). Like beads in a long necklace, these monomers link by covalent bonds to form long polymers (poly-= "many"). There are many examples of monomers and polymers among the organic compounds.

Monomers form polymers by engaging in dehydration synthesis (see [link]). As was noted earlier, this reaction results in the release of a molecule of water. Each monomer contributes: One gives up a hydrogen atom and the other gives up a hydroxyl group. Polymers are split into monomers by hydrolysis (-lysis = "rupture"). The bonds between their monomers are broken, via the donation of a molecule of water, which contributes a hydrogen atom to one monomer and a hydroxyl group to the other.

Carbohydrates

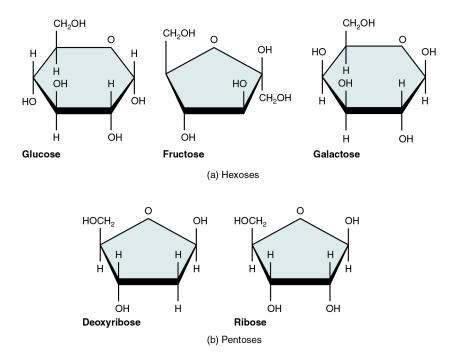
The term carbohydrate means "hydrated carbon." Recall that the root hydro- indicates water. A **carbohydrate** is a molecule composed of carbon, hydrogen, and oxygen; in most carbohydrates, hydrogen and oxygen are found in the same two-to-one relative proportions they have in water. In fact, the chemical formula for a "generic" molecule of carbohydrate is $(CH_2O)_n$.

Carbohydrates are referred to as saccharides, a word meaning "sugars." Three forms are important in the body. Monosaccharides are the monomers of carbohydrates. Disaccharides (di- = "two") are made up of two monomers. **Polysaccharides** are the polymers, and can consist of hundreds to thousands of monomers.

Monosaccharides

A **monosaccharide** is a monomer of carbohydrates. Five monosaccharides are important in the body. Three of these are the hexose sugars, so called because they each contain six atoms of carbon. These are glucose, fructose, and galactose, shown in [link]a. The remaining monosaccharides are the two pentose sugars, each of which contains five atoms of carbon. They are ribose and deoxyribose, shown in [link]b.

Five Important Monosaccharides

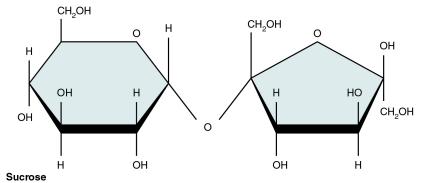


Disaccharides

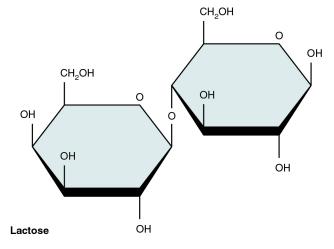
A **disaccharide** is a pair of monosaccharides. Disaccharides are formed via dehydration synthesis, and the bond linking them is referred to as a glycosidic bond (glyco-= "sugar"). Three disaccharides (shown in [link]) are important to humans. These are sucrose, commonly referred to as table sugar; lactose, or milk sugar; and maltose, or malt sugar. As you can tell from their common names, you consume these in your diet; however, your body cannot use them directly. Instead, in the digestive tract, they are split into their component monosaccharides via hydrolysis.

Three Important Disaccharides

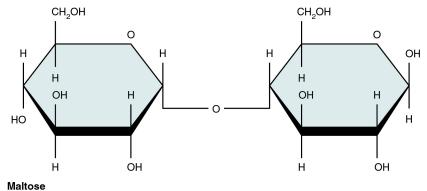
(a) The monosaccharides glucose and fructose bond to form sucrose



(b) The monosaccharides galactose and glucose bond to form lactose.



(c) Two glucose monosaccharides bond to form maltose.



All three important disaccharides form by dehydration synthesis.

Note:



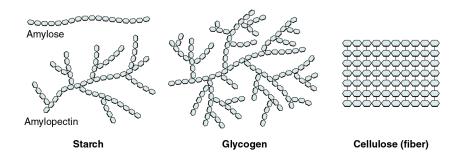
Watch this <u>video</u> to observe the formation of a disaccharide. What happens when water encounters a glycosidic bond?

Polysaccharides

Polysaccharides can contain a few to a thousand or more monosaccharides. Three are important to the body ([link]):

- Starches are polymers of glucose. They occur in long chains called amylose or branched chains called amylopectin, both of which are stored in plant-based foods and are relatively easy to digest.
- Glycogen is also a polymer of glucose, but it is stored in the tissues of animals, especially in the muscles and liver. It is not considered a dietary carbohydrate because very little glycogen remains in animal tissues after slaughter; however, the human body stores excess glucose as glycogen, again, in the muscles and liver.
- Cellulose, a polysaccharide that is the primary component of the cell wall of green plants, is the component of plant food referred to as "fiber". In humans, cellulose/fiber is not digestible; however, dietary fiber has many health benefits. It helps you feel full so you eat less, it promotes a healthy digestive tract, and a diet high in fiber is thought to reduce the risk of heart disease and possibly some forms of cancer.

Three Important Polysaccharides



Three important polysaccharides are starches, glycogen, and fiber.

Functions of Carbohydrates

The body obtains carbohydrates from plant-based foods. Grains, fruits, and legumes and other vegetables provide most of the carbohydrate in the human diet, although lactose is found in dairy products.

Although most body cells can break down other organic compounds for fuel, all body cells can use glucose. Moreover, nerve cells (neurons) in the brain, spinal cord, and through the peripheral nervous system, as well as red blood cells, can use only glucose for fuel. In the breakdown of glucose for energy, molecules of adenosine triphosphate, better known as ATP, are produced. **Adenosine triphosphate (ATP)** is composed of a ribose sugar, an adenine base, and three phosphate groups. ATP releases free energy when its phosphate bonds are broken, and thus supplies ready energy to the cell. More ATP is produced in the presence of oxygen (O_2) than in pathways that do not use oxygen. The overall reaction for the conversion of the energy in glucose to energy stored in ATP can be written:

Equation:

$$C_6H_{12}O_6 + 6 O_2 \rightarrow 6 CO_2 + 6 H_2O + ATP$$

In addition to being a critical fuel source, carbohydrates are present in very small amounts in cells' structure. For instance, some carbohydrate

molecules bind with proteins to produce glycoproteins, and others combine with lipids to produce glycolipids, both of which are found in the membrane that encloses the contents of body cells.

Lipids

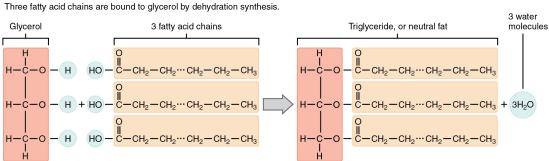
A **lipid** is one of a highly diverse group of compounds made up mostly of hydrocarbons. The few oxygen atoms they contain are often at the periphery of the molecule. Their nonpolar hydrocarbons make all lipids hydrophobic. In water, lipids do not form a true solution, but they may form an emulsion, which is the term for a mixture of solutions that do not mix well.

Triglycerides

A **triglyceride** is one of the most common dietary lipid groups, and the type found most abundantly in body tissues. This compound, which is commonly referred to as a fat, is formed from the synthesis of two types of molecules ([link]):

- A glycerol backbone at the core of triglycerides, consists of three carbon atoms.
- Three fatty acids, long chains of hydrocarbons with a carboxyl group and a methyl group at opposite ends, extend from each of the carbons of the glycerol.

Triglycerides

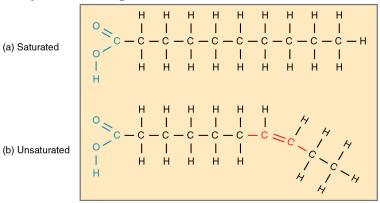


Triglycerides are composed of glycerol attached to three fatty acids via dehydration synthesis. Notice that glycerol gives up a hydrogen atom, and the carboxyl groups on the fatty acids each give up a hydroxyl group.

Triglycerides form via dehydration synthesis. Glycerol gives up hydrogen atoms from its hydroxyl groups at each bond, and the carboxyl group on each fatty acid chain gives up a hydroxyl group. A total of three water molecules are thereby released.

Fatty acid chains that have no double carbon bonds anywhere along their length and therefore contain the maximum number of hydrogen atoms are called saturated fatty acids. These straight, rigid chains pack tightly together and are solid or semi-solid at room temperature ([link]a). Butter and lard are examples, as is the fat found on a steak or in your own body. In contrast, fatty acids with one double carbon bond are kinked at that bond ([link]b). These monounsaturated fatty acids are therefore unable to pack together tightly, and are liquid at room temperature. Polyunsaturated fatty acids contain two or more double carbon bonds, and are also liquid at room temperature. Plant oils such as olive oil typically contain both mono- and polyunsaturated fatty acids.

Fatty Acid Shapes



The level of saturation of a fatty acid affects its shape. (a) Saturated fatty acid

chains are straight. (b) Unsaturated fatty acid chains are kinked.

Whereas a diet high in saturated fatty acids increases the risk of heart disease, a diet high in unsaturated fatty acids is thought to reduce the risk. This is especially true for the omega-3 unsaturated fatty acids found in cold-water fish such as salmon. These fatty acids have their first double carbon bond at the third hydrocarbon from the methyl group (referred to as the omega end of the molecule).

Finally, *trans* fatty acids found in some processed foods, including some stick and tub margarines, are thought to be even more harmful to the heart and blood vessels than saturated fatty acids. *Trans* fats are created from unsaturated fatty acids (such as corn oil) when chemically treated to produce partially hydrogenated fats.

As a group, triglycerides are a major fuel source for the body. When you are resting or asleep, a majority of the energy used to keep you alive is derived from triglycerides stored in your fat (adipose) tissues. Triglycerides also fuel long, slow physical activity such as gardening or hiking, and contribute a modest percentage of energy for vigorous physical activity. Dietary fat also assists the absorption and transport of the nonpolar fat-soluble vitamins A, D, E, and K. Additionally, stored body fat protects and cushions the body's bones and internal organs, and acts as insulation to retain body heat.

Fatty acids are also components of glycolipids, which are sugar-fat compounds found in the cell membrane. Lipoproteins are compounds in which the hydrophobic triglycerides are packaged in protein envelopes for transport in body fluids.

Phospholipids

As its name suggests, a **phospholipid** is a bond between the glycerol component of a lipid and a phosphorous molecule. In fact, phospholipids are similar in structure to triglycerides. However, instead of having three

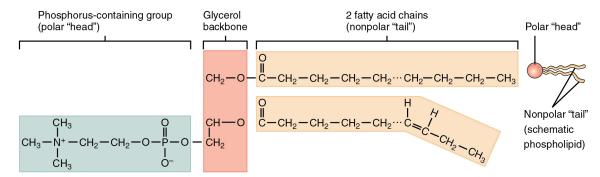
fatty acids, a phospholipid is generated from a diglyceride, a glycerol with just two fatty acid chains ([link]). The third binding site on the glycerol is taken up by the phosphate group, which in turn is attached to a polar "head" region of the molecule. Recall that triglycerides are nonpolar and hydrophobic. This still holds for the fatty acid portion of a phospholipid compound. However, the phosphate-containing group at the head of the compound is polar and thereby hydrophilic. In other words, one end of the molecule can interact with oil, and the other end with water. This makes phospholipids ideal emulsifiers, compounds that help disperse fats in aqueous liquids, and enables them to interact with both the watery interior of cells and the watery solution outside of cells as components of the cell membrane.

Other Important Lipids

(a) Phospholipids

Two fatty acid chains and a phosphorus-containing group are attached to the glycerol backbone.

Example: Phosphatidylcholine



(b) Sterols

Four interlocking hydrocarbon rings from a steroid.

Example: Cholesterol (cholesterol is the basis for all steroids formed in the body)

(c) Prostaglandins

(a) Phospholipids are composed of two fatty acids, glycerol, and a phosphate group. (b) Sterols are ring-shaped lipids. Shown here is cholesterol. (c) Prostaglandins are derived from unsaturated fatty acids. Prostaglandin E2 (PGE2) includes hydroxyl and carboxyl groups.

Steroids

A **steroid** compound (referred to as a sterol) has as its foundation a set of four hydrocarbon rings bonded to a variety of other atoms and molecules (see [link]b). Although both plants and animals synthesize sterols, the type that makes the most important contribution to human structure and function is cholesterol, which is synthesized by the liver in humans and animals and is also present in most animal-based foods. Like other lipids, cholesterol's hydrocarbons make it hydrophobic; however, it has a polar hydroxyl head that is hydrophilic. Cholesterol is an important component of bile acids, compounds that help emulsify dietary fats. In fact, the word root cholerefers to bile. Cholesterol is also a building block of many hormones, signaling molecules that the body releases to regulate processes at distant sites. Finally, like phospholipids, cholesterol molecules are found in the cell membrane, where their hydrophobic and hydrophilic regions help regulate the flow of substances into and out of the cell.

Prostaglandins

Like a hormone, a **prostaglandin** is one of a group of signaling molecules, but prostaglandins are derived from unsaturated fatty acids (see [link]c). One reason that the omega-3 fatty acids found in fish are beneficial is that they stimulate the production of certain prostaglandins that help regulate aspects of blood pressure and inflammation, and thereby reduce the risk for heart disease. Prostaglandins also sensitize nerves to pain. One class of pain-relieving medications called nonsteroidal anti-inflammatory drugs (NSAIDs) works by reducing the effects of prostaglandins.

Proteins

You might associate proteins with muscle tissue, but in fact, proteins are critical components of all tissues and organs. A **protein** is an organic molecule composed of amino acids linked by peptide bonds. Proteins include the keratin in the epidermis of skin that protects underlying tissues, the collagen found in the dermis of skin, in bones, and in the meninges that

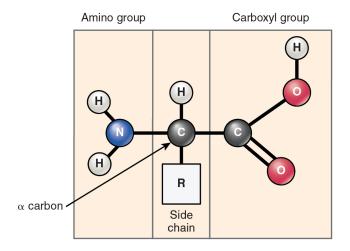
cover the brain and spinal cord. Proteins are also components of many of the body's functional chemicals, including digestive enzymes in the digestive tract, antibodies, the neurotransmitters that neurons use to communicate with other cells, and the peptide-based hormones that regulate certain body functions (for instance, growth hormone). While carbohydrates and lipids are composed of hydrocarbons and oxygen, all proteins also contain nitrogen (N), and many contain sulfur (S), in addition to carbon, hydrogen, and oxygen.

Microstructure of Proteins

Proteins are polymers made up of nitrogen-containing monomers called amino acids. An **amino acid** is a molecule composed of an amino group and a carboxyl group, together with a variable side chain. Just 20 different amino acids contribute to nearly all of the thousands of different proteins important in human structure and function. Body proteins contain a unique combination of a few dozen to a few hundred of these 20 amino acid monomers. All 20 of these amino acids share a similar structure ([link]). All consist of a central carbon atom to which the following are bonded:

- a hydrogen atom
- an alkaline (basic) amino group NH₂ (see [link])
- an acidic carboxyl group COOH (see [link])
- a variable group

Structure of an Amino Acid



Notice that all amino acids contain both an acid (the carboxyl group) and a base (the amino group) (amine = "nitrogen-containing"). For this reason, they make excellent buffers, helping the body regulate acid—base balance. What distinguishes the 20 amino acids from one another is their variable group, which is referred to as a side chain or an R-group. This group can vary in size and can be polar or nonpolar, giving each amino acid its unique characteristics. For example, the side chains of two amino acids—cysteine and methionine—contain sulfur. Sulfur does not readily participate in hydrogen bonds, whereas all other amino acids do. This variation influences the way that proteins containing cysteine and methionine are assembled.

Amino acids join via dehydration synthesis to form protein polymers ([link]). The unique bond holding amino acids together is called a peptide bond. A **peptide bond** is a covalent bond between two amino acids that forms by dehydration synthesis. A peptide, in fact, is a very short chain of amino acids. Strands containing fewer than about 100 amino acids are generally referred to as polypeptides rather than proteins.

Peptide Bond

Different amino acids join together to form peptides, polypeptides, or proteins via dehydration synthesis. The bonds between the amino acids are peptide bonds.

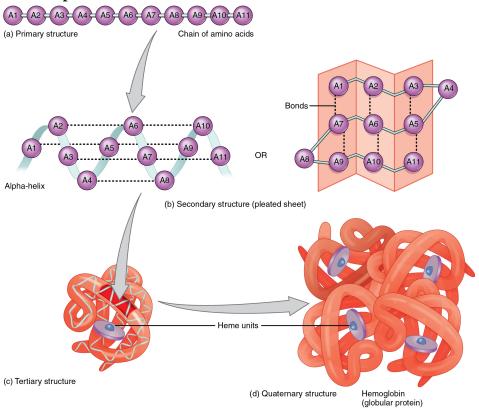
The body is able to synthesize most of the amino acids from components of other molecules; however, nine cannot be synthesized and have to be consumed in the diet. These are known as the essential amino acids.

Free amino acids available for protein construction are said to reside in the amino acid pool within cells. Structures within cells use these amino acids when assembling proteins. If a particular essential amino acid is not available in sufficient quantities in the amino acid pool, however, synthesis of proteins containing it can slow or even cease.

Shape of Proteins

Just as a fork cannot be used to eat soup and a spoon cannot be used to spear meat, a protein's shape is essential to its function. A protein's shape is determined, most fundamentally, by the sequence of amino acids of which it is made ([link]a). The sequence is called the primary structure of the protein.

The Shape of Proteins



(a) The primary structure is the sequence of amino acids that make up the polypeptide chain. (b) The secondary structure, which can take the form of an alpha-helix or a beta-pleated sheet, is maintained by hydrogen bonds between amino acids in different regions of the original polypeptide strand. (c) The tertiary structure occurs as a result of further folding and bonding of the secondary structure. (d) The quaternary structure occurs as a result of interactions between two or more tertiary subunits. The example shown here is hemoglobin, a protein in red blood cells which transports oxygen to body tissues.

Although some polypeptides exist as linear chains, most are twisted or folded into more complex secondary structures that form when bonding

occurs between amino acids with different properties at different regions of the polypeptide. The most common secondary structure is a spiral called an alpha-helix. If you were to take a length of string and simply twist it into a spiral, it would not hold the shape. Similarly, a strand of amino acids could not maintain a stable spiral shape without the help of hydrogen bonds, which create bridges between different regions of the same strand (see [link]b). Less commonly, a polypeptide chain can form a beta-pleated sheet, in which hydrogen bonds form bridges between different regions of a single polypeptide that has folded back upon itself, or between two or more adjacent polypeptide chains.

The secondary structure of proteins further folds into a compact three-dimensional shape, referred to as the protein's tertiary structure (see [link]c). In this configuration, amino acids that had been very distant in the primary chain can be brought quite close via hydrogen bonds or, in proteins containing cysteine, via disulfide bonds. A **disulfide bond** is a covalent bond between sulfur atoms in a polypeptide. Often, two or more separate polypeptides bond to form an even larger protein with a quaternary structure (see [link]d). The polypeptide subunits forming a quaternary structure can be identical or different. For instance, hemoglobin, the protein found in red blood cells is composed of four tertiary polypeptides, two of which are called alpha chains and two of which are called beta chains.

When they are exposed to extreme heat, acids, bases, and certain other substances, proteins will denature. **Denaturation** is a change in the structure of a molecule through physical or chemical means. Denatured proteins lose their functional shape and are no longer able to carry out their jobs. An everyday example of protein denaturation is the curdling of milk when acidic lemon juice is added.

The contribution of the shape of a protein to its function can hardly be exaggerated. For example, the long, slender shape of protein strands that make up muscle tissue is essential to their ability to contract (shorten) and relax (lengthen). As another example, bones contain long threads of a protein called collagen that acts as scaffolding upon which bone minerals are deposited. These elongated proteins, called fibrous proteins, are strong and durable and typically hydrophobic.

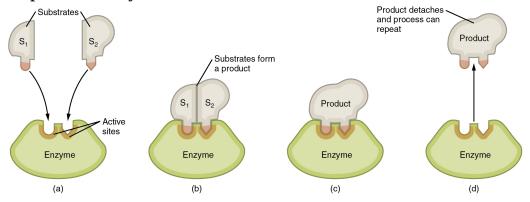
In contrast, globular proteins are globes or spheres that tend to be highly reactive and are hydrophilic. The hemoglobin proteins packed into red blood cells are an example (see [link]d); however, globular proteins are abundant throughout the body, playing critical roles in most body functions. Enzymes, introduced earlier as protein catalysts, are examples of this. The next section takes a closer look at the action of enzymes.

Proteins Function as Enzymes

If you were trying to type a paper, and every time you hit a key on your laptop there was a delay of six or seven minutes before you got a response, you would probably get a new laptop. In a similar way, without enzymes to catalyze chemical reactions, the human body would be nonfunctional. It functions only because enzymes function.

Enzymatic reactions—chemical reactions catalyzed by enzymes—begin when substrates bind to the enzyme. A **substrate** is a reactant in an enzymatic reaction. This occurs on regions of the enzyme known as active sites ([link]). Any given enzyme catalyzes just one type of chemical reaction. This characteristic, called specificity, is due to the fact that a substrate with a particular shape and electrical charge can bind only to an active site corresponding to that substrate.

Steps in an Enzymatic Reaction



(a) Substrates approach active sites on enzyme. (b) Substrates bind to active sites, producing an enzyme—substrate complex. (c) Changes internal to the enzyme—

substrate complex facilitate interaction of the substrates. (d) Products are released and the enzyme returns to its original form, ready to facilitate another enzymatic reaction.

Binding of a substrate produces an enzyme—substrate complex. It is likely that enzymes speed up chemical reactions in part because the enzyme—substrate complex undergoes a set of temporary and reversible changes that cause the substrates to be oriented toward each other in an optimal position to facilitate their interaction. This promotes increased reaction speed. The enzyme then releases the product(s), and resumes its original shape. The enzyme is then free to engage in the process again, and will do so as long as substrate remains.

Other Functions of Proteins

Advertisements for protein bars, powders, and shakes all say that protein is important in building, repairing, and maintaining muscle tissue, but the truth is that proteins contribute to all body tissues, from the skin to the brain cells. Also, certain proteins act as hormones, chemical messengers that help regulate body functions, For example, growth hormone is important for skeletal growth, among other roles.

As was noted earlier, the basic and acidic components enable proteins to function as buffers in maintaining acid—base balance, but they also help regulate fluid—electrolyte balance. Proteins attract fluid, and a healthy concentration of proteins in the blood, the cells, and the spaces between cells helps ensure a balance of fluids in these various "compartments." Moreover, proteins in the cell membrane help to transport electrolytes in and out of the cell, keeping these ions in a healthy balance. Like lipids, proteins can bind with carbohydrates. They can thereby produce glycoproteins or proteoglycans, both of which have many functions in the body.

The body can use proteins for energy when carbohydrate and fat intake is inadequate, and stores of glycogen and adipose tissue become depleted. However, since there is no storage site for protein except functional tissues, using protein for energy causes tissue breakdown, and results in body wasting.

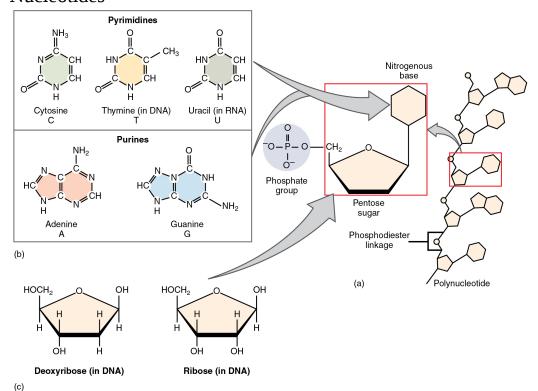
Nucleotides

The fourth type of organic compound important to human structure and function are the nucleotides ([link]). A **nucleotide** is one of a class of organic compounds composed of three subunits:

- one or more phosphate groups
- a pentose sugar: either deoxyribose or ribose
- a nitrogen-containing base: adenine, cytosine, guanine, thymine, or uracil

Nucleotides can be assembled into nucleic acids (DNA or RNA) or the energy compound adenosine triphosphate.

Nucleotides



(a) The building blocks of all nucleotides are one or more phosphate groups, a pentose sugar, and a nitrogencontaining base. (b) The nitrogen-containing bases of nucleotides. (c) The two pentose sugars of DNA and RNA.

Nucleic Acids

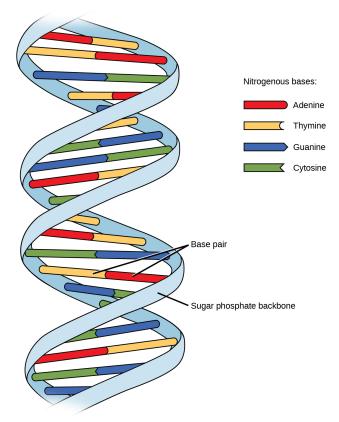
The nucleic acids differ in their type of pentose sugar. **Deoxyribonucleic acid (DNA)** is nucleotide that stores genetic information. DNA contains deoxyribose (so-called because it has one less atom of oxygen than ribose) plus one phosphate group and one nitrogen-containing base. The "choices" of base for DNA are adenine, cytosine, guanine, and thymine. **Ribonucleic acid (RNA)** is a ribose-containing nucleotide that helps manifest the genetic code as protein. RNA contains ribose, one phosphate group, and one nitrogen-containing base, but the "choices" of base for RNA are adenine, cytosine, guanine, and uracil.

The nitrogen-containing bases adenine and guanine are classified as purines. A **purine** is a nitrogen-containing molecule with a double ring structure, which accommodates several nitrogen atoms. The bases cytosine, thymine (found in DNA only) and uracil (found in RNA only) are pyramidines. A **pyramidine** is a nitrogen-containing base with a single ring structure

Bonds formed by dehydration synthesis between the pentose sugar of one nucleic acid monomer and the phosphate group of another form a "backbone," from which the components' nitrogen-containing bases protrude. In DNA, two such backbones attach at their protruding bases via hydrogen bonds. These twist to form a shape known as a double helix ([link]). The sequence of nitrogen-containing bases within a strand of DNA form the genes that act as a molecular code instructing cells in the assembly of amino acids into proteins. Humans have almost 22,000 genes in their DNA, locked up in the 46 chromosomes inside the nucleus of each cell

(except red blood cells which lose their nuclei during development). These genes carry the genetic code to build one's body, and are unique for each individual except identical twins.

DNA



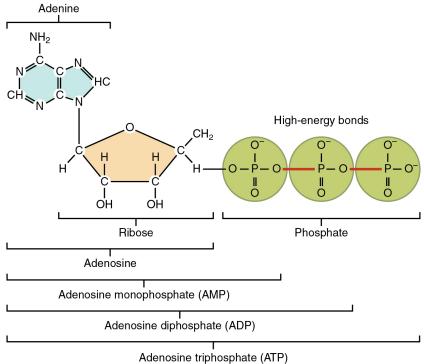
In the DNA double helix, two strands attach via hydrogen bonds between the bases of the component nucleotides.

In contrast, RNA consists of a single strand of sugar-phosphate backbone studded with bases. Messenger RNA (mRNA) is created during protein synthesis to carry the genetic instructions from the DNA to the cell's protein manufacturing plants in the cytoplasm, the ribosomes.

Adenosine Triphosphate

The nucleotide adenosine triphosphate (ATP), is composed of a ribose sugar, an adenine base, and three phosphate groups ([link]). ATP is classified as a high energy compound because the two covalent bonds linking its three phosphates store a significant amount of potential energy. In the body, the energy released from these high energy bonds helps fuel the body's activities, from muscle contraction to the transport of substances in and out of cells to anabolic chemical reactions.

Structure of Adenosine Triphosphate (ATP)



When a phosphate group is cleaved from ATP, the products are adenosine diphosphate (ADP) and inorganic phosphate (P_i). This hydrolysis reaction can be written:

Equation:

$$ATP + H_2O \ \rightarrow \ ADP + P_i + energy$$

Removal of a second phosphate leaves adenosine monophosphate (AMP) and two phosphate groups. Again, these reactions also liberate the energy that had been stored in the phosphate-phosphate bonds. They are reversible,

too, as when ADP undergoes phosphorylation. **Phosphorylation** is the addition of a phosphate group to an organic compound, in this case, resulting in ATP. In such cases, the same level of energy that had been released during hydrolysis must be reinvested to power dehydration synthesis.

Cells can also transfer a phosphate group from ATP to another organic compound. For example, when glucose first enters a cell, a phosphate group is transferred from ATP, forming glucose phosphate ($C_6H_{12}O_6$ —P) and ADP. Once glucose is phosphorylated in this way, it can be stored as glycogen or metabolized for immediate energy.

Chapter Review

Organic compounds essential to human functioning include carbohydrates, lipids, proteins, and nucleotides. These compounds are said to be organic because they contain both carbon and hydrogen. Carbon atoms in organic compounds readily share electrons with hydrogen and other atoms, usually oxygen, and sometimes nitrogen. Carbon atoms also may bond with one or more functional groups such as carboxyls, hydroxyls, aminos, or phosphates. Monomers are single units of organic compounds. They bond by dehydration synthesis to form polymers, which can in turn be broken by hydrolysis.

Carbohydrate compounds provide essential body fuel. Their structural forms include monosaccharides such as glucose, disaccharides such as lactose, and polysaccharides, including starches (polymers of glucose), glycogen (the storage form of glucose), and fiber. All body cells can use glucose for fuel. It is converted via an oxidation-reduction reaction to ATP.

Lipids are hydrophobic compounds that provide body fuel and are important components of many biological compounds. Triglycerides are the most abundant lipid in the body, and are composed of a glycerol backbone attached to three fatty acid chains. Phospholipids are compounds composed of a diglyceride with a phosphate group attached at the molecule's head. The result is a molecule with polar and nonpolar regions. Steroids are lipids

formed of four hydrocarbon rings. The most important is cholesterol. Prostaglandins are signaling molecules derived from unsaturated fatty acids.

Proteins are critical components of all body tissues. They are made up of monomers called amino acids, which contain nitrogen, joined by peptide bonds. Protein shape is critical to its function. Most body proteins are globular. An example is enzymes, which catalyze chemical reactions.

Nucleotides are compounds with three building blocks: one or more phosphate groups, a pentose sugar, and a nitrogen-containing base. DNA and RNA are nucleic acids that function in protein synthesis. ATP is the body's fundamental molecule of energy transfer. Removal or addition of phosphates releases or invests energy.

Glossary

adenosine triphosphate (ATP)

nucleotide containing ribose and an adenine base that is essential in energy transfer

amino acid

building block of proteins; characterized by an amino and carboxyl functional groups and a variable side-chain

carbohydrate

class of organic compounds built from sugars, molecules containing carbon, hydrogen, and oxygen in a 1-2-1 ratio

denaturation

change in the structure of a molecule through physical or chemical means

deoxyribonucleic acid (DNA)

deoxyribose-containing nucleotide that stores genetic information

disaccharide

pair of carbohydrate monomers bonded by dehydration synthesis via a glycosidic bond

disulfide bond

covalent bond formed within a polypeptide between sulfide groups of sulfur-containing amino acids, for example, cysteine

functional group

group of atoms linked by strong covalent bonds that tends to behave as a distinct unit in chemical reactions with other atoms

lipid

class of nonpolar organic compounds built from hydrocarbons and distinguished by the fact that they are not soluble in water

macromolecule

large molecule formed by covalent bonding

monosaccharide

monomer of carbohydrate; also known as a simple sugar

nucleotide

class of organic compounds composed of one or more phosphate groups, a pentose sugar, and a base

peptide bond

covalent bond formed by dehydration synthesis between two amino acids

phospholipid

a lipid compound in which a phosphate group is combined with a diglyceride

phosphorylation

addition of one or more phosphate groups to an organic compound

polysaccharide

compound consisting of more than two carbohydrate monomers bonded by dehydration synthesis via glycosidic bonds

prostaglandin

lipid compound derived from fatty acid chains and important in regulating several body processes

protein

class of organic compounds that are composed of many amino acids linked together by peptide bonds

purine

nitrogen-containing base with a double ring structure; adenine and guanine

pyrimidine

nitrogen-containing base with a single ring structure; cytosine, thiamine, and uracil

ribonucleic acid (RNA)

ribose-containing nucleotide that helps manifest the genetic code as protein

steroid

(also, sterol) lipid compound composed of four hydrocarbon rings bonded to a variety of other atoms and molecules

substrate

reactant in an enzymatic reaction

triglyceride

lipid compound composed of a glycerol molecule bonded with three fatty acid chains

OU Human Physiology: Homeostasis Introduction class="introduction" Blood Pressure

A proficiency in anatomy and physiology is fundamental to any career in the health professions.

(credit:

Bryan

Mason/flickr
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Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Distinguish between anatomy and physiology
- Describe the structure of the body, from simplest to most complex, in terms of the six levels of organization
- Identify the functional characteristics of human life
- Identify the four requirements for human survival
- Define homeostasis and its importance to normal human functioning
- Explain positive and negative feedback and the role of each player in feedback systems
- Compare and contrast the tissue types, their unique structural properties, and their functions
- Compare and contrast the three cell to cell junctions
- Compare and contrast an exocrine and an endocrine gland

Though you may approach a course in anatomy and physiology strictly as a requirement for your field of study, the knowledge you gain in this course will serve you well in many aspects of your life. An understanding of anatomy and physiology is not only fundamental to any career in the health professions, but it can also benefit your own health. Familiarity with the human body can help you make healthful choices and prompt you to take appropriate action when signs of illness arise. Your knowledge in this field will help you understand news about nutrition, medications, medical devices, and procedures and help you understand genetic or infectious diseases. At some point, everyone will have a problem with some aspect of his or her body and your knowledge can help you to be a better parent, spouse, partner, friend, colleague, or caregiver.

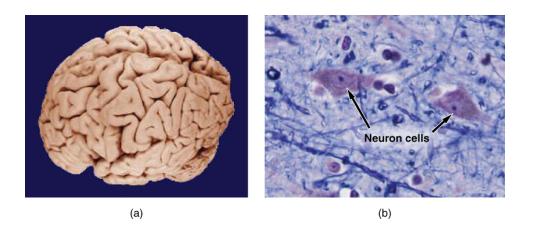
This chapter begins with an overview of anatomy and physiology and a preview of the body regions and functions. It then covers the characteristics of life and how the body works to maintain stable conditions organization and organ systems of humans.

OU Human Physiology: Overview of Anatomy and Physiology By the end of this section, you will be able to:

• • Distinguish between anatomy and physiology

Human **anatomy** is the scientific study of the body's structures. Some of these structures are very small and can only be observed and analyzed with the assistance of a microscope. Other larger structures can readily be seen, manipulated, measured, and weighed. The word "anatomy" comes from a Greek root that means "to cut apart." Human anatomy was first studied by observing the exterior of the body and observing the wounds of soldiers and other injuries. Later, physicians were allowed to dissect bodies of the dead to augment their knowledge. When a body is dissected, its structures are cut apart in order to observe their physical attributes and their relationships to one another. Dissection is still used in medical schools, anatomy courses, and in pathology labs. In order to observe structures in living people, however, a number of imaging techniques have been developed. These techniques allow clinicians to visualize structures inside the living body such as a cancerous tumor or a fractured bone.

Like most scientific disciplines, anatomy has areas of specialization. **Gross anatomy** is the study of the larger structures of the body, those visible without the aid of magnification ([link]a). Macro- means "large," thus, gross anatomy is also referred to as macroscopic anatomy. In contrast, micro- means "small," and **microscopic anatomy** is the study of structures that can be observed only with the use of a microscope or other magnification devices ([link]b). Microscopic anatomy includes cytology, the study of cells and histology, the study of tissues. As the technology of microscopes has advanced, anatomists have been able to observe smaller and smaller structures of the body, from slices of large structures like the heart, to the three-dimensional structures of large molecules in the body. **Gross and Microscopic Anatomy**



(a) Gross anatomy considers large structures such as the brain. (b) Microscopic anatomy can deal with the same structures, though at a different scale. This is a micrograph of nerve cells from the brain. LM × 1600. (credit a: "WriterHound"/Wikimedia Commons; credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Anatomists take two general approaches to the study of the body's structures: regional and systemic. **Regional anatomy** is the study of the interrelationships of all of the structures in a specific body region, such as the abdomen. Studying regional anatomy helps us appreciate the interrelationships of body structures, such as how muscles, nerves, blood vessels, and other structures work together to serve a particular body region. In contrast, **systemic anatomy** is the study of the structures that make up a discrete body system—that is, a group of structures that work together to perform a unique body function. For example, a systemic anatomical study of the muscular system would consider all of the skeletal muscles of the body.

Whereas anatomy is about structure, physiology is about function. Human **physiology** is the scientific study of the chemistry and physics of the structures of the body and the ways in which they work together to support the functions of life. Much of the study of physiology centers on the body's tendency toward homeostasis. **Homeostasis** is the state of steady internal

conditions maintained by living things. The study of physiology certainly includes observation, both with the naked eye and with microscopes, as well as manipulations and measurements. However, current advances in physiology usually depend on carefully designed laboratory experiments that reveal the functions of the many structures and chemical compounds that make up the human body.

Like anatomists, physiologists typically specialize in a particular branch of physiology. For example, neurophysiology is the study of the brain, spinal cord, and nerves and how these work together to perform functions as complex and diverse as vision, movement, and thinking. Physiologists may work from the organ level (exploring, for example, what different parts of the brain do) to the molecular level (such as exploring how an electrochemical signal travels along nerves).

Form is closely related to function in all living things. For example, the thin flap of your eyelid can snap down to clear away dust particles and almost instantaneously slide back up to allow you to see again. At the microscopic level, the arrangement and function of the nerves and muscles that serve the eyelid allow for its quick action and retreat. At a smaller level of analysis, the function of these nerves and muscles likewise relies on the interactions of specific molecules and ions. Even the three-dimensional structure of certain molecules is essential to their function.

Your study of anatomy and physiology will make more sense if you continually relate the form of the structures you are studying to their function. In fact, it can be somewhat frustrating to attempt to study anatomy without an understanding of the physiology that a body structure supports. Imagine, for example, trying to appreciate the unique arrangement of the bones of the human hand if you had no conception of the function of the hand. Fortunately, your understanding of how the human hand manipulates tools—from pens to cell phones—helps you appreciate the unique alignment of the thumb in opposition to the four fingers, making your hand a structure that allows you to pinch and grasp objects and type text messages.

Chapter Review

Human anatomy is the scientific study of the body's structures. In the past, anatomy has primarily been studied via observing injuries, and later by the dissection of anatomical structures of cadavers, but in the past century, computer-assisted imaging techniques have allowed clinicians to look inside the living body. Human physiology is the scientific study of the chemistry and physics of the structures of the body. Physiology explains how the structures of the body work together to maintain life. It is difficult to study structure (anatomy) without knowledge of function (physiology). The two disciplines are typically studied together because form and function are closely related in all living things.

Glossary

anatomy

science that studies the form and composition of the body's structures

gross anatomy

study of the larger structures of the body, typically with the unaided eye; also referred to macroscopic anatomy

homeostasis

steady state of body systems that living organisms maintain

microscopic anatomy

study of very small structures of the body using magnification

physiology

science that studies the chemistry, biochemistry, and physics of the body's functions

regional anatomy

study of the structures that contribute to specific body regions

systemic anatomy

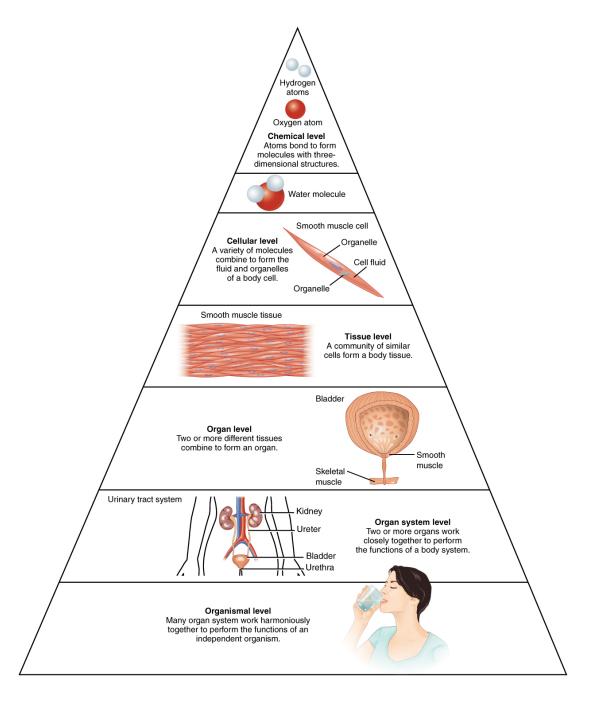
study of the structures that contribute to specific body systems

OU Human Physiology: Structural Organization of the Human Body By the end of this section, you will be able to:

- Describe the structure of the human body in terms of six levels of organization
- List the eleven organ systems of the human body and identify at least one organ and one major function of each

Before you begin to study the different structures and functions of the human body, it is helpful to consider its basic architecture; that is, how its smallest parts are assembled into larger structures. It is convenient to consider the structures of the body in terms of fundamental levels of organization that increase in complexity: subatomic particles, atoms, molecules, organelles, cells, tissues, organs, organ systems, organisms and biosphere ([link]).

Levels of Structural Organization of the Human Body



The organization of the body often is discussed in terms of six distinct levels of increasing complexity, from the smallest chemical building blocks to a unique human organism.

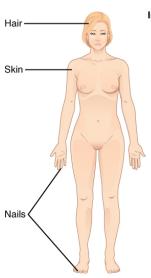
The Levels of Organization

To study the chemical level of organization, scientists consider the simplest building blocks of matter: subatomic particles, atoms and molecules. All matter in the universe is composed of one or more unique pure substances called elements, familiar examples of which are hydrogen, oxygen, carbon, nitrogen, calcium, and iron. The smallest unit of any of these pure substances (elements) is an atom. Atoms are made up of subatomic particles such as the proton, electron and neutron. Two or more atoms combine to form a molecule, such as the water molecules, proteins, and sugars found in living things. Molecules are the chemical building blocks of all body structures.

A **cell** is the smallest independently functioning unit of a living organism. Even bacteria, which are extremely small, independently-living organisms, have a cellular structure. Each bacterium is a single cell. All living structures of human anatomy contain cells, and almost all functions of human physiology are performed in cells or are initiated by cells.

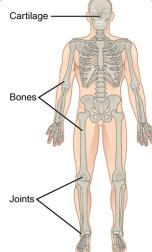
A human cell typically consists of flexible membranes that enclose cytoplasm, a water-based cellular fluid together with a variety of tiny functioning units called **organelles**. In humans, as in all organisms, cells perform all functions of life. A **tissue** is a group of many similar cells (though sometimes composed of a few related types) that work together to perform a specific function. An **organ** is an anatomically distinct structure of the body composed of two or more tissue types. Each organ performs one or more specific physiological functions. An **organ system** is a group of organs that work together to perform major functions or meet physiological needs of the body.

This book covers eleven distinct organ systems in the human body ([link] and [link]). Assigning organs to organ systems can be imprecise since organs that "belong" to one system can also have functions integral to another system. In fact, most organs contribute to more than one system. Organ Systems of the Human Body



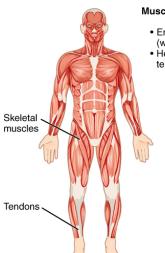
Integumentary System

- Encloses internal body structures
- Site of many sensory receptors



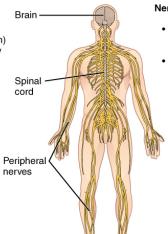
Skeletal System

- Supports the bodyEnables movement (with muscular system)



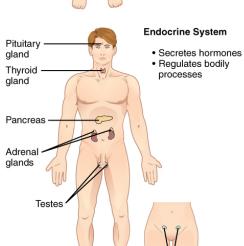
Muscular System

- Enables movement (with skeletal system)
- Helps maintain body temperature

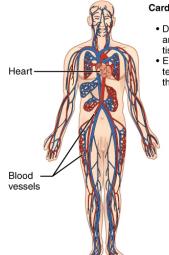


Nervous System

- Detects and processes sensory information
- Activates bodily responses



Ovaries

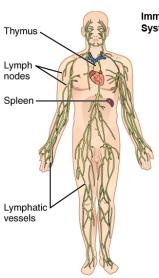


Cardiovascular System

- Delivers oxygen and nutrients to tissues
- Equalizes temperature in the body

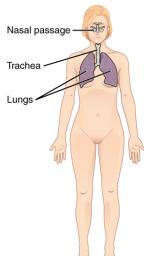
Organs that work together are grouped into organ systems.

Organ Systems of the Human Body (continued)



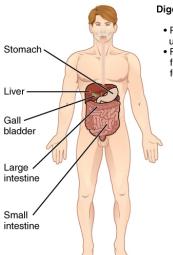
Immune and Lymphatic System

- Returns fluid to blood
- Defends against pathogens



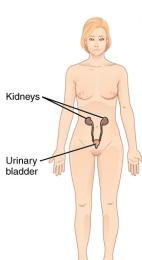
Respiratory System

- Removes carbon dioxide from the body
- Delivers oxygen to blood



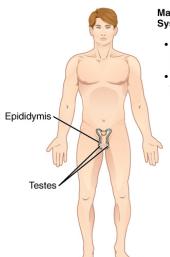
Digestive System

- Processes food for use by the bodyRemoves wastes
- Removes wastes from undigested food



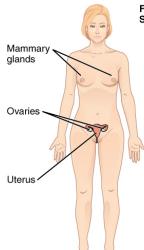
Urinary System

- Controls water balance in the body
- Removes wastes from blood and excretes them



Male Reproductive System

- Produces sex hormones and gametes
- gametes
 Delivers gametes
 to female



Female Reproductive System

- Produces sex hormones and gametes
- Supports embryo/ fetus until birth
- Produces milk for infant

Organs that work together are grouped into organ systems.

The organism level is the highest level of organization. An **organism** is a living being that has a cellular structure and that can independently perform all physiologic functions necessary for life. In multicellular organisms, including humans, all cells, tissues, organs, and organ systems of the body work together to maintain the life and health of the organism.

Chapter Review

Life processes of the human body are maintained at several levels of structural organization. These include the chemical, cellular, tissue, organ, organ system, and the organism level. Higher levels of organization are built from lower levels. Therefore, molecules combine to form cells, cells combine to form tissues, tissues combine to form organs, organs combine to form organ systems, and organ systems combine to form organisms.

Glossary

cell

smallest independently functioning unit of all organisms; in animals, a cell contains cytoplasm, composed of fluid and organelles

organ

functionally distinct structure composed of two or more types of tissues

organ system

group of organs that work together to carry out a particular function

organelle

structural unit of cells that carry out specific functions of the cells

organism

living being that has a cellular structure and that can independently perform all physiologic functions necessary for life

tissue

group of similar or closely related cells that act together to perform a specific function

OU Human Physiology: Functions of Human Life By the end of this section, you will be able to:

Identify the functional characteristics of human life

The different organ systems each have different functions and therefore unique roles to perform in physiology. These many functions can be summarized in terms of a few that we might consider definitive of human life: organization, metabolism, responsiveness, movement, development, and reproduction.

Organization

A human body consists of trillions of cells organized in a way that maintains distinct internal compartments. These compartments keep body cells separated from external environmental threats and keep the cells moist and nourished. They also separate internal body fluids from the countless microorganisms that grow on body surfaces, including the lining of certain tracts, or passageways. The intestinal tract, for example, is home to even more bacteria cells than the total of all human cells in the body, yet these bacteria are outside the body and cannot be allowed to circulate freely inside the body.

Cells, for example, have a cell membrane (also referred to as the plasma membrane) that keeps the intracellular environment—the fluids and organelles—separate from the extracellular environment. Blood vessels keep blood inside a closed circulatory system, and nerves and muscles are wrapped in connective tissue sheaths that separate them from surrounding structures. In the chest and abdomen, a variety of internal membranes keep major organs such as the lungs, heart, and kidneys separate from others.

The body's largest organ system is the integumentary system, which includes the skin and its associated structures, such as hair and nails. The surface tissue of skin is a barrier that protects internal structures and fluids from potentially harmful microorganisms and other toxins.

Metabolism

The first law of thermodynamics holds that energy can neither be created nor destroyed—it can only change form. Your basic function as an organism is to consume (ingest) energy and molecules in the foods you eat, convert some of it into fuel for movement, sustain your body functions, and build and maintain your body structures. There are two types of reactions that accomplish this: **anabolism** and **catabolism**.

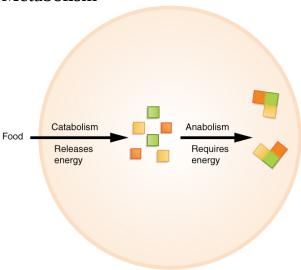
- **Anabolism** is the process whereby smaller, simpler molecules are combined into larger, more complex substances. Your body can assemble, by utilizing energy, the complex chemicals it needs by combining small molecules derived from the foods you eat ([link]a)
- **Catabolism** is the process by which larger more complex substances are broken down into smaller simpler molecules. Catabolism releases energy. The complex molecules found in foods are broken down so the body can use their parts to assemble the structures and substances needed for life.([link]b)

Metabolic Reactions

(a) In this example of an anabolic reaction, two amino acids (subunits) come together to form a dipeptide (biomolecule) and a water molecule. (b) In this example of a catabolic reaction water is used to break down the dipeptide (biomolecule) into individual amino acids (subunits).

Taken together, these two processes are called metabolism. **Metabolism** is the sum of all anabolic and catabolic reactions that take place in the body ([link]). Both anabolism and catabolism occur simultaneously and continuously to keep you alive.

Metabolism



Anabolic reactions are building reactions, and they consume energy. Catabolic reactions break materials down and release energy. Metabolism includes both anabolic and catabolic reactions.

Every cell in your body makes use of a chemical compound, **adenosine triphosphate (ATP)**, to store and release energy. The cell stores energy in the synthesis (anabolism) of ATP, then moves the ATP molecules to the location where energy is needed to fuel cellular activities. Then the ATP is broken down (catabolism) and a controlled amount of energy is released, which is used by the cell to perform a particular job.

Note:



View this <u>animation</u> to learn more about metabolic processes. What kind of catabolism occurs in the heart?

Responsiveness

Responsiveness is the ability of an organism to adjust to changes in its internal and external environments. An example of responsiveness to external stimuli could include moving toward sources of food and water and away from perceived dangers. Changes in an organism's internal environment, such as increased body temperature, can cause the responses of sweating and the dilation of blood vessels in the skin in order to decrease body temperature, as shown by the runners in [link].

Movement

Human movement includes not only actions at the joints of the body, but also the motion of individual organs and even individual cells. As you read these words, red and white blood cells are moving throughout your body, muscle cells are contracting and relaxing to maintain your posture and to focus your vision, and glands are secreting chemicals to regulate body functions. Your body is coordinating the action of entire muscle groups to enable you to move air into and out of your lungs, to push blood throughout your body, and to propel the food you have eaten through your digestive tract. Consciously, of course, you contract your skeletal muscles to move the bones of your skeleton to get from one place to another (as the runners are doing in [link]), and to carry out all of the activities of your daily life. Marathon Runners



Runners demonstrate two characteristics of living humans—responsiveness and movement. Anatomic structures and physiological processes allow runners to coordinate the action of muscle groups and sweat in response to rising internal body temperature. (credit: Phil Roeder/flickr)

Development, growth and reproduction

Development is all of the changes the body goes through in life. Development includes the processes of differentiation, growth, and renewal.

Differentiation is the process whereby unspecialized cells become specialized in both structure and function. After conception, when a female's egg is fertilized by a male's sperm cell, the fertilized egg begins to multiply, initially into a cluster of identical unspecialized cells. As cell division continues, however, the cells begin to undergo differentiation into distinct tissue layers, and eventually into all of the specialized cells, tissues, and organs of the fetus. The progression from the undifferentiated cells to

certain types of differentiated cells goes on throughout life, even in the bodies of adults.

Growth is the increase in body size. Humans, like all multicellular organisms, grow by increasing the number of existing cells, increasing the amount of non-cellular material around cells (such as mineral deposits in bone), and, within very narrow limits, increasing the size of existing cells.

Renewal is the formation of new cells for growth, repair, or replacement. In some organ systems, such as the digestive system, worn-out cells are constantly replaced throughout life. Some other specialized cells, however have only a limited capacity for renewal. This is true, for example, of nerve cells of the nervous system. When death of such cells is extensive (as can occur in a stroke, which causes cell death in the brain), the system can fail. Because the body is an integrated whole, failure of a body system can ultimately lead to the death of the organism.

Reproduction is the formation of a new organism from parent organisms. In humans, reproduction is carried out by the male and female reproductive systems. Because death will come to all complex organisms, without reproduction, the line of organisms would end.

Chapter Review

Most processes that occur in the human body are not consciously controlled. They occur continuously to build, maintain, and sustain life. These processes include: organization, in terms of the maintenance of essential body boundaries; metabolism, including energy transfer via anabolic and catabolic reactions; responsiveness; movement; and growth, differentiation, reproduction, and renewal.

Glossary

adenosine triphosphate (ATP)

adenosine triphosphate, a nucleotide composed of a sugar (ribose), base (Adenosine), and three phosphates; ATP is a temporary carrier of energy that is derived from Adenosine diphosphates

anabolism

assembly of more complex molecules from simpler molecules

catabolism

breaking down of more complex molecules into simpler molecules

development

changes an organism goes through during its life

differentiation

process by which unspecialized cells become specialized in structure and function

growth

process of increasing in size

metabolism

sum of all of the body's chemical reactions

renewal

process by which worn-out cells are replaced

reproduction

process by which new organisms are generated

responsiveness

ability of an organisms or a system to adjust to changes in conditions

OU Human Physiology: Requirements for Human Life By the end of this section, you will be able to:

• Identify the four requirements for human survival

Humans have been adapting to life on Earth for at least the past 200,000 years. Earth and its atmosphere have provided us with air to breathe, water to drink, and food to eat, but these are not the only requirements for survival. Although you may rarely think about it, you also cannot live outside of a certain range of temperature and pressure that the surface of our planet and its atmosphere provides. The next sections explore these four requirements of life.

Oxygen

Atmospheric air is only about 20 percent oxygen, but that oxygen is a key component of the chemical reactions that keep the body alive, including the reactions that produce ATP. Brain cells are especially sensitive to lack of oxygen because of their requirement for a high-and-steady production of ATP. Brain damage is likely within five minutes without oxygen, and death is likely within ten minutes.

Nutrients

A **nutrient** is a substance in foods and beverages that is essential to human survival. The three basic classes of nutrients are water, the energy-yielding and body-building nutrients, and the micronutrients (vitamins and minerals).

The most critical nutrient is water. Depending on the environmental temperature and our state of health, we may be able to survive for only a few days without water. The body's functional chemicals are dissolved and transported in water, and the chemical reactions of life take place in water. Moreover, water is the largest component of cells, blood, and the fluid between cells, and water makes up about 70 percent of an adult's body mass. Water also helps regulate our internal temperature and cushions, protects, and lubricates joints and many other body structures.

The energy-yielding nutrients are primarily carbohydrates and lipids, while proteins mainly supply the amino acids that are the building blocks of the body itself. You ingest these in plant and animal foods and beverages, and the digestive system breaks them down into molecules small enough to be absorbed. The breakdown products of carbohydrates and lipids can then be used in the metabolic processes that convert them to ATP. Although you might feel as if you are starving after missing a single meal, you can survive without consuming the energy-yielding nutrients for at least several weeks.

Water and the energy-yielding nutrients are also referred to as macronutrients because the body needs them in large amounts. In contrast, micronutrients are vitamins and minerals. These elements and compounds participate in many essential chemical reactions and processes, such nerve impulses, and some, such as calcium, also contribute to the body's structure. Your body can store some of the micronutrients in its tissues, and draw on those reserves if you fail to consume them in your diet for a few days or weeks. Some others micronutrients, such as vitamin C and most of the B vitamins, are water-soluble and cannot be stored, so you need to consume them every day or two.

Narrow Range of Temperature

You have probably seen news stories about athletes who died of heat stroke, or hikers who died of exposure to cold. Such deaths occur because the chemical reactions upon which the body depends can only take place within a narrow range of body temperature, from just below to just above 37°C (98.6°F). When body temperature rises well above or drops well below normal, certain proteins (enzymes) that facilitate chemical reactions lose their normal structure and their ability to function and the chemical reactions of metabolism cannot proceed.

That said, the body can respond effectively to short-term exposure to heat ([link]) or cold. One of the body's responses to heat is, of course, sweating. As sweat evaporates from skin, it removes some thermal energy from the body, cooling it. Adequate water (from the extracellular fluid in the body) is necessary to produce sweat, so adequate fluid intake is essential to balance that loss during the sweat response. Not surprisingly, the sweat response is

much less effective in a humid environment because the air is already saturated with water. Thus, the sweat on the skin's surface is not able to evaporate, and internal body temperature can get dangerously high.

Extreme Heat



Humans adapt to some degree to repeated exposure to high temperatures. (credit: McKay Savage/flickr)

The body can also respond effectively to short-term exposure to cold. One response to cold is shivering, which is random muscle movement that generates heat. Another response is increased breakdown of stored energy to generate heat. When that energy reserve is depleted, however, and the core temperature begins to drop significantly, red blood cells will lose their ability to give up oxygen, denying the brain of this critical component of ATP production. This lack of oxygen can cause confusion, lethargy, and eventually loss of consciousness and death. The body responds to cold by reducing blood circulation to the extremities, the hands and feet, in order to prevent blood from cooling there and so that the body's core can stay warm. Even when core body temperature remains stable, however, tissues exposed to severe cold, especially the fingers and toes, can develop frostbite when blood flow to the extremities has been much reduced. This form of tissue

damage can be permanent and lead to gangrene, requiring amputation of the affected region.

Note:

Everyday Connection

Controlled Hypothermia

As you have learned, the body continuously engages in coordinated physiological processes to maintain a stable temperature. In some cases, however, overriding this system can be useful, or even life-saving. Hypothermia is the clinical term for an abnormally low body temperature (hypo- = "below" or "under"). Controlled hypothermia is clinically induced hypothermia performed in order to reduce the metabolic rate of an organ or of a person's entire body.

Controlled hypothermia often is used, for example, during open-heart surgery because it decreases the metabolic needs of the brain, heart, and other organs, reducing the risk of damage to them. When controlled hypothermia is used clinically, the patient is given medication to prevent shivering. The body is then cooled to 25–32°C (79–89°F). The heart is stopped and an external heart-lung pump maintains circulation to the patient's body. The heart is cooled further and is maintained at a temperature below 15°C (60°F) for the duration of the surgery. This very cold temperature helps the heart muscle to tolerate its lack of blood supply during the surgery.

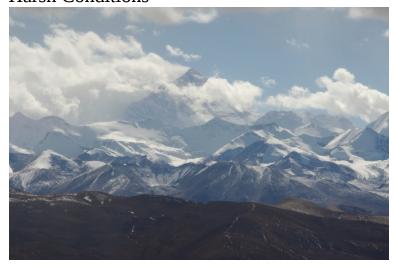
Some emergency department physicians use controlled hypothermia to reduce damage to the heart in patients who have suffered a cardiac arrest. In the emergency department, the physician induces coma and lowers the patient's body temperature to approximately 91 degrees. This condition, which is maintained for 24 hours, slows the patient's metabolic rate. Because the patient's organs require less blood to function, the heart's workload is reduced.

Narrow Range of Atmospheric Pressure

Pressure is a force exerted by a substance that is in contact with another substance. Atmospheric pressure is pressure exerted by the mixture of gases (primarily nitrogen and oxygen) in the Earth's atmosphere. Although you may not perceive it, atmospheric pressure is constantly pressing down on your body. This pressure keeps gases within your body, such as the gaseous nitrogen in body fluids, dissolved. If you were suddenly ejected from a space ship above Earth's atmosphere, you would go from a situation of normal pressure to one of very low pressure. The pressure of the nitrogen gas in your blood would be much higher than the pressure of nitrogen in the space surrounding your body. As a result, the nitrogen gas in your blood would expand, forming bubbles that could block blood vessels and even cause cells to break apart.

Atmospheric pressure does more than just keep blood gases dissolved. Your ability to breathe—that is, to take in oxygen and release carbon dioxide—also depends upon a precise atmospheric pressure. Altitude sickness occurs in part because the atmosphere at high altitudes exerts less pressure, reducing the exchange of these gases, and causing shortness of breath, confusion, headache, lethargy, and nausea. Mountain climbers carry oxygen to reduce the effects of both low oxygen levels and low barometric pressure at higher altitudes ([link]).

Harsh Conditions



Climbers on Mount Everest must accommodate extreme cold, low oxygen levels, and low barometric pressure in an

environment hostile to human life. (credit: Melanie Ko/flickr)

Note:

Homeostatic Imbalances

Decompression Sickness

Decompression sickness (DCS) is a condition in which gases dissolved in the blood or in other body tissues are no longer dissolved following a reduction in pressure on the body. This condition affects underwater divers who surface from a deep dive too quickly, and it can affect pilots flying at high altitudes in planes with unpressurized cabins. Divers often call this condition "the bends," a reference to joint pain that is a symptom of DCS. In all cases, DCS is brought about by a reduction in barometric pressure. At high altitude, barometric pressure is much less than on Earth's surface because pressure is produced by the weight of the column of air above the body pressing down on the body. The very great pressures on divers in deep water are likewise from the weight of a column of water pressing down on the body. For divers, DCS occurs at normal barometric pressure (at sea level), but it is brought on by the relatively rapid decrease of pressure as divers rise from the high pressure conditions of deep water to the now low, by comparison, pressure at sea level. Not surprisingly, diving in deep mountain lakes, where barometric pressure at the surface of the lake is less than that at sea level is more likely to result in DCS than diving in water at sea level.

In DCS, gases dissolved in the blood (primarily nitrogen) come rapidly out of solution, forming bubbles in the blood and in other body tissues. This occurs because when pressure of a gas over a liquid is decreased, the amount of gas that can remain dissolved in the liquid also is decreased. It is air pressure that keeps your normal blood gases dissolved in the blood. When pressure is reduced, less gas remains dissolved. You have seen this in effect when you open a carbonated drink. Removing the seal of the bottle reduces the pressure of the gas over the liquid. This in turn causes

bubbles as dissolved gases (in this case, carbon dioxide) come out of solution in the liquid.

The most common symptoms of DCS are pain in the joints, with headache and disturbances of vision occurring in 10 percent to 15 percent of cases. Left untreated, very severe DCS can result in death. Immediate treatment is with pure oxygen. The affected person is then moved into a hyperbaric chamber. A hyperbaric chamber is a reinforced, closed chamber that is pressurized to greater than atmospheric pressure. It treats DCS by repressurizing the body so that pressure can then be removed much more gradually. Because the hyperbaric chamber introduces oxygen to the body at high pressure, it increases the concentration of oxygen in the blood. This has the effect of replacing some of the nitrogen in the blood with oxygen, which is easier to tolerate out of solution.

The dynamic pressure of body fluids is also important to human survival. For example, blood pressure, which is the pressure exerted by blood as it flows within blood vessels, must be great enough to enable blood to reach all body tissues, and yet low enough to ensure that the delicate blood vessels can withstand the friction and force of the pulsating flow of pressurized blood.

Chapter Review

Humans cannot survive for more than a few minutes without oxygen, for more than several days without water, and for more than several weeks without carbohydrates, lipids, proteins, vitamins, and minerals. Although the body can respond to high temperatures by sweating and to low temperatures by shivering and increased fuel consumption, long-term exposure to extreme heat and cold is not compatible with survival. The body requires a precise atmospheric pressure to maintain its gases in solution and to facilitate respiration—the intake of oxygen and the release of carbon dioxide. Humans also require blood pressure high enough to ensure that blood reaches all body tissues but low enough to avoid damage to blood vessels.

Glossary

nutrient

chemical obtained from foods and beverages that is critical to human survival

pressure

force exerted by a substance in contact with another substance

OU Human Physiology: Homeostasis By the end of this section, you will be able to:

- Define homeostasis and its importance to normal human functioning
- Explain the purpose of both positive and negative feedback systems
- Illustrate an understanding of each component of both feedback systems

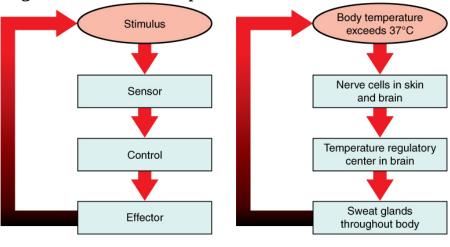
Maintaining homeostasis requires that the body continuously monitor its internal conditions. From body temperature to blood pressure to levels of certain nutrients, each physiological condition has a particular set point. A **set point** is the physiological value around which the normal range fluctuates. A **normal range** is the restricted set of values that is optimally healthful and stable. For example, the set point for normal human body temperature is approximately 37°C (98.6°F) Physiological parameters, such as body temperature and blood pressure, tend to fluctuate within a normal range a few degrees above and below that point. Control centers in the brain play roles in regulating physiological parameters and keeping them within the normal range. As the body works to maintain homeostasis, any significant deviation from the normal range will be resisted and homeostasis restored through a process called negative feedback. **Negative feedback** is a mechanism that prevents a physiological response from going beyond the normal range by reversing the action once the normal range is exceeded. The maintenance of homeostasis by negative feedback goes on throughout the body at all times, and an understanding of negative feedback is thus fundamental to an understanding of human physiology.

Negative Feedback

A negative feedback system has three basic components ([link]a). A **sensor**, also referred to a receptor, is a component of a feedback system that monitors a physiological value known as a **controlled variable** or regulated variable. This value is reported to the integrating center. The **integrating center** is the component in a feedback system that compares the value to the normal range. If the value deviates too much from the set point, then the control center activates an effector. An **effector** is the component in a

feedback system that causes a change to reverse the situation and return the value to the normal range.

Negative Feedback Loop



(a) Negative feedback loop

(b) Body temperature regulation

In a negative feedback loop, a stimulus—a deviation from a set point—is resisted through a physiological process that returns the body to homeostasis. (a) A negative feedback loop has four basic parts. (b) Body temperature is regulated by negative feedback.

In order to set the system in motion, a stimulus must drive a physiological parameter beyond its normal range (that is, beyond homeostasis). This stimulus is "heard" by a specific sensor. For example, in the control of blood glucose, specific endocrine cells in the pancreas detect excess glucose (the stimulus) in the bloodstream. These pancreatic beta cells respond to the increased level of blood glucose by releasing the hormone insulin into the bloodstream. The insulin signals skeletal muscle fibers, fat cells (adipocytes), and liver cells to take up the excess glucose, removing it from the bloodstream. As glucose concentration in the bloodstream drops, the decrease in concentration—the actual negative feedback—is detected by pancreatic alpha cells, and insulin release stops. This prevents blood sugar levels from continuing to drop below the normal range.

Humans have a similar temperature regulation feedback system that works by promoting either heat loss or heat gain ([link]b). When the brain's temperature regulation center receives data from the sensors indicating that the body's temperature exceeds its normal range, it stimulates a cluster of brain cells referred to as the "heat-loss center." This stimulation has three major effects:

- Blood vessels in the skin begin to dilate allowing more blood from the body core to flow to the surface of the skin allowing the heat to radiate into the environment.
- As blood flow to the skin increases, sweat glands are activated to increase their output. As the sweat evaporates from the skin surface into the surrounding air, it takes heat with it.
- The depth of respiration increases, and a person may breathe through an open mouth instead of through the nasal passageways. This further increases heat loss from the lungs.

In contrast, activation of the brain's heat-gain center by exposure to cold reduces blood flow to the skin, and blood returning from the limbs is diverted into a network of deep veins. This arrangement traps heat closer to the body core and restricts heat loss. If heat loss is severe, the brain triggers an increase in random signals to skeletal muscles, causing them to contract and producing shivering. The muscle contractions of shivering release heat while using up ATP. The brain triggers the thyroid gland in the endocrine system to release thyroid hormone, which increases metabolic activity and heat production in cells throughout the body. The brain also signals the adrenal glands to release epinephrine (adrenaline), a hormone that causes the breakdown of glycogen into glucose, which can be used as an energy source. The breakdown of glycogen into glucose also results in increased metabolism and heat production.

Note:			



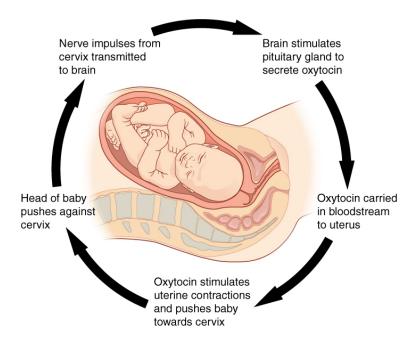
Water concentration in the body is critical for proper functioning. A person's body retains very tight control on water levels without conscious control by the person. Watch this <u>video</u> to learn more about water concentration in the body. Which organ has primary control over the amount of water in the body?

Positive Feedback

Positive feedback intensifies a change in the body's physiological condition rather than reversing it. A deviation from the normal range results in more change, and the system moves farther away from the normal range. Positive feedback in the body is normal only when there is a definite end point. Childbirth and the body's response to blood loss are two examples of positive feedback loops that are normal but are activated only when needed.

Childbirth at full term is an example of a situation in which the maintenance of the existing body state is not desired. Enormous changes in the mother's body are required to expel the baby at the end of pregnancy. And the events of childbirth, once begun, must progress rapidly to a conclusion or the life of the mother and the baby are at risk. The extreme muscular work of labor and delivery are the result of a positive feedback system ([link]).

Positive Feedback Loop



Normal childbirth is driven by a positive feedback loop. A positive feedback loop results in a change in the body's status, rather than a return to homeostasis.

The first contractions of labor (the stimulus) push the baby toward the cervix (the lowest part of the uterus). The cervix contains stretch-sensitive nerve cells that monitor the degree of stretching (the sensors). These nerve cells send messages to the brain, which in turn causes the pituitary gland at the base of the brain to release the hormone oxytocin into the bloodstream. Oxytocin causes stronger contractions of the smooth muscles in of the uterus (the effectors), pushing the baby further down the birth canal. This causes even greater stretching of the cervix. The cycle of stretching, oxytocin release, and increasingly more forceful contractions stops only when the baby is born. At this point, the stretching of the cervix halts, stopping the release of oxytocin.

A second example of positive feedback centers on reversing extreme damage to the body. Following a penetrating wound, the most immediate threat is excessive blood loss. Less blood circulating means reduced blood pressure and reduced perfusion (penetration of blood) to the brain and other vital organs. If perfusion is severely reduced, vital organs will shut down and the person will die. The body responds to this potential catastrophe by releasing substances in the injured blood vessel wall that begin the process of blood clotting. As each step of clotting occurs, it stimulates the release of more clotting substances. This accelerates the processes of clotting and sealing off the damaged area. Clotting is contained in a local area based on the tightly controlled availability of clotting proteins. This is an adaptive, life-saving cascade of events.

Chapter Review

Homeostasis is the activity of cells throughout the body to maintain the physiological state within a narrow range that is compatible with life. Homeostasis is regulated by negative feedback loops and, much less frequently, by positive feedback loops. Both have the same components of a stimulus, sensor, control center, and effector; however, negative feedback loops work to prevent an excessive response to the stimulus, whereas positive feedback loops intensify the response until an end point is reached.

Glossary

controlled variable

a physiological value that is regulated to stay with certain limits

effector

organ that can cause a change in a value

integrating center

compares values to their normal range; deviations cause the activation of an effector

negative feedback

homeostatic mechanism that tends to stabilize an upset in the body's physiological condition by preventing an excessive response to a stimulus, typically as the stimulus is removed

normal range

range of values around the set point that do not cause a reaction by the control center

positive feedback

mechanism that intensifies a change in the body's physiological condition in response to a stimulus

sensor

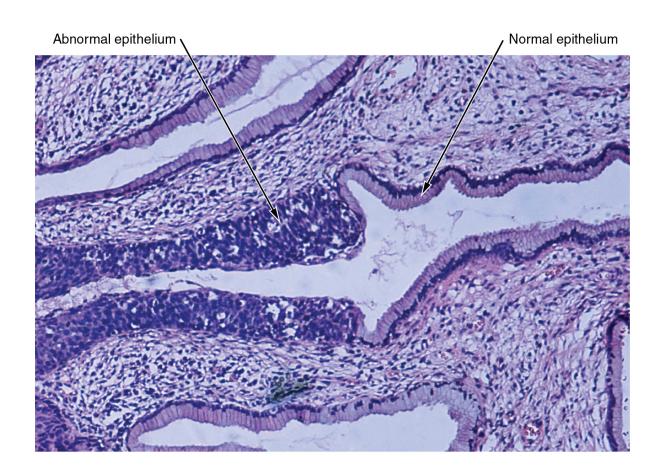
(also, receptor) reports a monitored physiological value to the control center

set point

ideal value for a physiological parameter; the level or small range within which a physiological parameter such as blood pressure is stable and optimally healthful, that is, within its parameters of homeostasis OU Human Physiology: Tissue Level Organization Introduction class="introduction"
Micrograph of Cervical Tissue

This figure is a view of the regular architecture of normal tissue contrasted with the irregular arrangement of cancerous cells.

(credit:
"Haymanj"/Wikimedi a Commons)



The body contains at least 200 distinct cell types. These cells contain essentially the same internal structures yet they vary enormously in shape and function. The different types of cells are not randomly distributed throughout the body; rather they occur in organized layers, a level of organization referred to as tissue. The micrograph that opens this chapter shows the high degree of organization among different types of cells in the tissue of the cervix. You can also see how that organization breaks down when cancer takes over the regular mitotic functioning of a cell.

The variety in shape reflects the many different roles that cells fulfill in your body. The human body starts as a single cell at fertilization. As this fertilized egg divides, it gives rise to trillions of cells, each built from the same blueprint, but organizing into tissues and becoming irreversibly committed to a developmental pathway.

OU Human Physiology: Types of Tissues By the end of this section, you will be able to:

- Identify the four main tissue types
- Discuss the functions of each tissue type

The term **tissue** is used to describe a group of cells found together in the body. The cells within a tissue share a common embryonic origin. Microscopic observation reveals that the cells in a tissue share morphological features and are arranged in an orderly pattern that achieves the tissue's functions. From the evolutionary perspective, tissues appear in more complex organisms. For example, multicellular protists, ancient eukaryotes, do not have cells organized into tissues.

Although there are many types of cells in the human body, they are organized into four broad categories of tissues: epithelial, connective, muscle, and nervous. Each of these categories is characterized by specific functions that contribute to the overall health and maintenance of the body. A disruption of the structure is a sign of injury or disease. Such changes can be detected through **histology**, the microscopic study of tissue appearance, organization, and function.

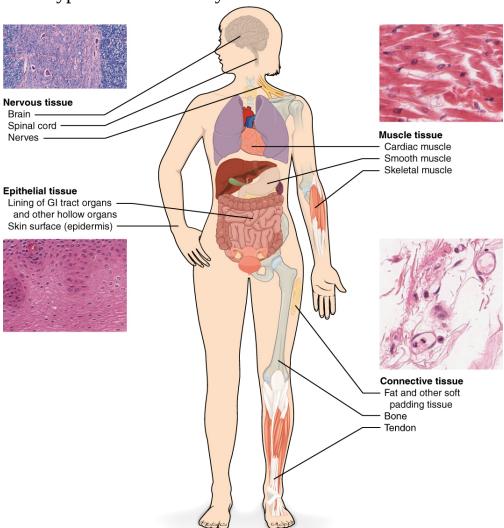
The Four Types of Tissues

Epithelial tissue, also referred to as epithelium, refers to the sheets of cells that cover exterior surfaces of the body, lines internal cavities and passageways, and forms certain glands. **Connective tissue**, as its name implies, binds the cells and organs of the body together and functions in the protection, support, and integration of all parts of the body. **Muscle tissue** is excitable, responding to stimulation and contracting to provide movement, and occurs as three major types: skeletal (voluntary) muscle, smooth muscle, and cardiac muscle in the heart. **Nervous tissue** is also excitable, allowing the propagation of electrochemical signals in the form of nerve impulses that communicate between different regions of the body ([link]).

The next level of organization is the organ, where several types of tissues come together to form a working unit. Just as knowing the structure and

function of cells helps you in your study of tissues, knowledge of tissues will help you understand how organs function. TEpithelial, connective, muscle, and nervous tissues will be discussed in this chapter.

Four Types of Tissue: Body



The four types of tissues are exemplified in nervous tissue, stratified squamous epithelial tissue, cardiac muscle tissue, and connective tissue in small intestine. Clockwise from nervous tissue, LM × 872, LM × 282, LM × 460, LM × 800. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

Chapter Review

The human body contains more than 200 types of cells that can all be classified into four types of tissues: epithelial, connective, muscle, and nervous. Epithelial tissues act as coverings controlling the movement of materials across the surface. Connective tissue integrates the various parts of the body and provides support and protection to organs. Muscle tissue allows the body to move. Nervous tissues propagate information.

The study of the shape and arrangement of cells in tissue is called histology. All cells and tissues in the body derive from three germ layers in the embryo: the ectoderm, mesoderm, and endoderm.

Different types of tissues form membranes that enclose organs, provide a friction-free interaction between organs, and keep organs together. Synovial membranes are connective tissue membranes that protect and line the joints. Epithelial membranes are formed from epithelial tissue attached to a layer of connective tissue. There are three types of epithelial membranes: mucous, which contain glands; serous, which secrete fluid; and cutaneous which makes up the skin.

Glossary

connective tissue

type of tissue that serves to hold in place, connect, and integrate the body's organs and systems

epithelial tissue

type of tissue that serves primarily as a covering or lining of body parts, protecting the body; it also functions in absorption, transport, and secretion

histology

microscopic study of tissue architecture, organization, and function

muscle tissue

type of tissue that is capable of contracting and generating tension in response to stimulation; produces movement.

nervous tissue

type of tissue that is capable of sending and receiving impulses through electrochemical signals.

tissue

group of similar or closely related cells that act together to perform a specific function

OU Human Physiology: Epithelial Tissue By the end of this section, you will be able to:

- Explain the structure and function of epithelial tissue
- Distinguish between tight junctions, desmosomes, and gap junctions
- Describe the structure and function of endocrine and exocrine glands and their respective secretions

Most epithelial tissues are essentially large sheets of cells covering all the surfaces of the body exposed to the outside world and lining the outside of organs. Epithelium also forms much of the glandular tissue of the body. Skin is not the only area of the body exposed to the outside. Other areas include the airways, the digestive tract, as well as the urinary and reproductive systems, all of which are lined by an epithelium. Hollow organs and body cavities that do not connect to the exterior of the body, which includes, blood vessels and serous membranes, are lined by endothelium (plural = endothelia), which is a type of epithelium.

All epithelia share some important structural and functional features. This tissue is highly cellular, with little or no extracellular material present between cells. Adjoining cells form a specialized intercellular connection between their cell membranes called a **cell junction**. The epithelial cells exhibit polarity with differences in structure and function between the exposed or **apical** facing surface of the cell and the basal surface close to the underlying body structures. The **basal lamina**, a mixture of glycoproteins and collagen, provides an attachment site for the epithelium, separating it from underlying connective tissue. The basal lamina attaches to a **reticular lamina**, which is secreted by the underlying connective tissue, forming a **basement membrane** that helps hold it all together.

Epithelial tissues are nearly completely avascular. For instance, no blood vessels cross the basement membrane to enter the tissue, and nutrients must come by diffusion or absorption from underlying tissues or the surface. Many epithelial tissues are capable of rapidly replacing damaged and dead cells. Sloughing off of damaged or dead cells is a characteristic of surface epithelium and allows our airways and digestive tracts to rapidly replace damaged cells with new cells.

Generalized Functions of Epithelial Tissue

Epithelial tissues provide the body's first line of protection from physical, chemical, and biological wear and tear. The cells of an epithelium act as gatekeepers of the body controlling permeability and allowing selective transfer of materials across a physical barrier. All substances that enter the body must cross an epithelium. Some epithelia often include structural features that allow the selective transport of molecules and ions across their cell membranes.

Many epithelial cells are capable of secretion and release mucous and specific chemical compounds onto their apical surfaces. The epithelium of the small intestine releases digestive enzymes, for example. Cells lining the respiratory tract secrete mucous that traps incoming microorganisms and particles. A glandular epithelium contains many secretory cells.

The Epithelial Cell

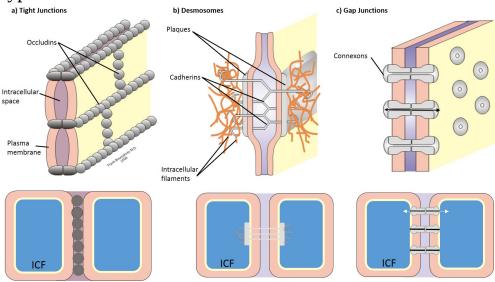
Epithelial cells are typically characterized by the polarized distribution of organelles and membrane-bound proteins between their basal and apical surfaces. Particular structures found in some epithelial cells are an adaptation to specific functions. Certain organelles are segregated to the basal sides, whereas other organelles and extensions, such as cilia, when present, are on the apical surface.

Cilia are microscopic extensions of the apical cell membrane that are supported by microtubules. They beat in unison and move fluids as well as trapped particles. Ciliated epithelium lines the ventricles of the brain where it helps circulate the cerebrospinal fluid. The ciliated epithelium of your airway forms a mucociliary escalator that sweeps particles of dust and pathogens trapped in the secreted mucous toward the throat. It is called an escalator because it continuously pushes mucous with trapped particles upward. In contrast, nasal cilia sweep the mucous blanket down towards your throat. In both cases, the transported materials are usually swallowed, and end up in the acidic environment of your stomach.

Cell to Cell Junctions

Cells of epithelia are closely connected and are not separated by intracellular material. Three basic types of connections allow varying degrees of interaction between the cells: tight junctions, desmosomes, and gap junctions ([link]).

Types of Cell Junctions



The three basic types of cell-to-cell junctions are (a) tight junctions, (b) desmosomes, and (c) gap junctions (credit: Frank Boumphrey CC BY SA 3.0)

At one end of the spectrum is the **tight junction** ([link]a). Tight junctions use integral membrane proteins called occludins to connect adjacent cells such that a nearly impermeable barrier seals the intercellular space which forcing most solutes to pass across the plasma membrane of the cells rather than through the intercellular space. These junctions are usually associated with epithelial cells that line the lumen of hollow organs, such as epithelial cells lining the wall of the gut or renal tubules.

Desmosomes ([link]b) are a type of anchoring junction that that helps tissues resist mechanical stress. Without desmosomes, cardiac muscle would pull apart when contracted and the urinary bladder would not be able

to stretch and fill with urine without tearing. These desmosomes consist of a glycoprotein plaque on the inside of each cell. Connected to this plaque are filaments that extend into the intracellular fluid and connect to intercellular filaments called cadherins. It is these cadherins that link together adjacent cells via the plaque. Desmosomes are found in many tissues including the epidermis, cardiac muscle, cervix of the uterus, and bladder.

In contrast with the tight and anchoring junctions, a **gap junction** ([link]c) forms an intercellular passageway via proteins called connexons between the membranes of adjacent cells to facilitate the movement of small molecules and ions between the cytoplasm of adjacent cells. These junctions allow electrical and metabolic coupling of adjacent cells, which coordinates function in large groups of cells.

Glandular Epithelium

A gland is a structure made up of one or more cells modified to synthesize and secrete chemical substances. Most glands consist of groups of epithelial cells. A gland can be classified as an **endocrine gland**, a ductless gland that releases secretions directly into surrounding tissues and fluids (endo-= "inside"), or an **exocrine gland** whose secretions leave through a duct that opens directly, or indirectly, to the external environment (exo-= "outside").

Endocrine Glands

The secretions of endocrine glands are called hormones. Hormones are released into the interstitial fluid, diffused into the bloodstream, and delivered to targets, in other words, cells that have receptors to bind the hormones. The endocrine system is part of a major regulatory system coordinating the regulation and integration of body responses. A few examples of endocrine glands include the anterior pituitary, thymus, adrenal cortex, and gonads.

Exocrine Glands

Exocrine glands release their contents through a duct that leads to the epithelial surface. Mucous, sweat, saliva, and breast milk are all examples of secretions from exocrine glands. They are all discharged through tubular ducts. Secretions into the lumen of the gastrointestinal tract, technically outside of the body, are of the exocrine category.

Chapter Review

In epithelial tissue, cells are closely packed with little or no extracellular matrix except for the basal lamina that separates the epithelium from underlying tissue. The main functions of epithelia are protection from the environment, coverage, secretion and excretion, absorption, and filtration. Cells are bound together by tight junctions that form an impermeable barrier. They can also be connected by gap junctions, which allow free exchange of soluble molecules between cells, and desmosomes. The different types of epithelial tissues are characterized by their cellular shapes and arrangements: squamous, cuboidal, or columnar epithelia. Single cell layers form simple epithelia, whereas stacked cells form stratified epithelia. Very few capillaries penetrate these tissues.

Glands are secretory tissues and organs that are derived from epithelial tissues. Exocrine glands release their products through ducts. Endocrine glands secrete hormones directly into the interstitial fluid and blood stream. Glands are classified both according to the type of secretion and by their structure. Merocrine glands secrete products as they are synthesized. Apocrine glands release secretions by pinching off the apical portion of the cell, whereas holocrine gland cells store their secretions until they rupture and release their contents. In this case, the cell becomes part of the secretion.

Glossary

apical

that part of a cell or tissue which, in general, faces an open space

basal lamina

thin extracellular layer that lies underneath epithelial cells and separates them from other tissues

basement membrane

in epithelial tissue, a thin layer of fibrous material that anchors the epithelial tissue to the underlying connective tissue; made up of the basal lamina and reticular lamina

cell junction

point of cell-to-cell contact that connects one cell to another in a tissue

endocrine gland

groups of cells that release chemical signals into the intercellular fluid to be picked up and transported to their target organs by blood

exocrine gland

group of epithelial cells that secrete substances through ducts that open to the skin or to internal body surfaces that lead to the exterior of the body

gap junction

allows cytoplasmic communications to occur between cells

reticular lamina

matrix containing collagen and elastin secreted by connective tissue; a component of the basement membrane

tight junction

forms an impermeable barrier between cells

OU Human Physiology: Connective Tissue Supports and Protects By the end of this section, you will be able to:

- Identify and distinguish between the types of connective tissue: proper, supportive, and fluid
- Explain the functions of connective tissues

As may be obvious from its name, one of the major functions of connective tissue is to connect tissues and organs. Unlike epithelial tissue, which is composed of cells closely packed with little or no extracellular space in between, connective tissue cells are dispersed in a **matrix**. The matrix usually includes a large amount of extracellular material produced by the connective tissue cells that are embedded within it. The matrix plays a major role in the functioning of this tissue. The major component of the matrix is a **ground substance** often crisscrossed by protein fibers. This ground substance is usually a fluid, but it can also be mineralized and solid, as in bones. Connective tissues come in a vast variety of forms, yet they typically have in common three characteristic components: cells, large amounts of amorphous ground substance, and protein fibers. The amount and structure of each component correlates with the function of the tissue, from the rigid ground substance in bones supporting the body to the inclusion of specialized cells; for example, a phagocytic cell that engulfs pathogens and also rids tissue of cellular debris.

Functions of Connective Tissues

Connective tissues perform many functions in the body, but most importantly, they support and connect other tissues; from the connective tissue sheath that surrounds muscle cells, to the tendons that attach muscles to bones, and to the skeleton that supports the positions of the body. Protection is another major function of connective tissue, in the form of fibrous capsules and bones that protect delicate organs and, of course, the skeletal system. Specialized cells in connective tissue defend the body from microorganisms that enter the body. Transport of fluid, nutrients, waste, and chemical messengers is ensured by specialized fluid connective tissues, such as blood and lymph. Adipose cells store surplus energy in the form of fat and contribute to the thermal insulation of the body.

Classification of Connective Tissues

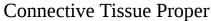
The three broad categories of connective tissue are classified according to the characteristics of their ground substance and the types of fibers found within the matrix ([link]). Connective tissue proper includes loose connective tissue and dense connective tissue. Both tissues have a variety of cell types and protein fibers suspended in a viscous ground substance. Dense connective tissue is reinforced by bundles of fibers that provide tensile strength, elasticity, and protection. In loose connective tissue, the fibers are loosely organized, leaving large spaces in between. Supportive connective tissue—bone and cartilage—provide structure and strength to the body and protect soft tissues. A few distinct cell types and densely packed fibers in a matrix characterize these tissues. In bone, the matrix is rigid and described as calcified because of the deposited calcium salts. In fluid connective tissue, in other words, lymph and blood, various specialized cells circulate in a watery fluid containing salts, nutrients, and dissolved proteins.

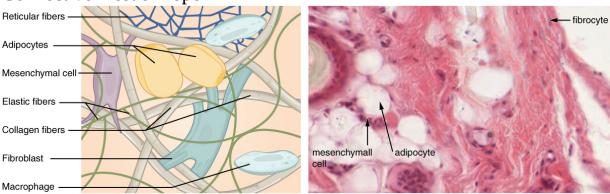
Connective Tissue Examples				
Connective tissue proper	Supportive connective tissue	Fluid connective tissue		
Loose connective tissue	Cartilage			
AreolarAdiposeReticular	HyalineFibrocartilageElastic	Blood		

Connective Tissue E		
Connective tissue proper	Supportive connective tissue	Fluid connective tissue
Dense connective tissue • Regular elastic • Irregular elastic	Bones • Compact bone • Cancellous bone	Lymph

Connective Tissue Proper

Fibroblasts are present in all connective tissue proper ([link]). Fibrocytes, adipocytes, and mesenchymal cells are fixed cells, which means they remain within the connective tissue. Other cells move in and out of the connective tissue in response to chemical signals. Macrophages, mast cells, lymphocytes, plasma cells, and phagocytic cells are found in connective tissue proper but are actually part of the immune system protecting the body.





Fibroblasts produce this fibrous tissue. Connective tissue proper includes the fixed cells fibrocytes, adipocytes, and mesenchymal cells.

LM × 400. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Cell Types

The most abundant cell in connective tissue proper is the **fibroblast**. Polysaccharides and proteins secreted by fibroblasts combine with extracellular fluids to produce a viscous ground substance that, with embedded fibrous proteins, forms the extra-cellular matrix. As you might expect, a **fibrocyte**, a less active form of fibroblast, is the second most common cell type in connective tissue proper.

Adipocytes are cells that store lipids as droplets that fill most of the cytoplasm. There are two basic types of adipocytes: white and brown. The brown adipocytes store lipids as many droplets, and have high metabolic activity. In contrast, white fat adipocytes store lipids as a single large drop and are metabolically less active. Their effectiveness at storing large amounts of fat is witnessed in obese individuals. The number and type of adipocytes depends on the tissue and location, and vary among individuals in the population.

The **mesenchymal cell** is a multipotent adult stem cell. These cells can differentiate into any type of connective tissue cells needed for repair and healing of damaged tissue.

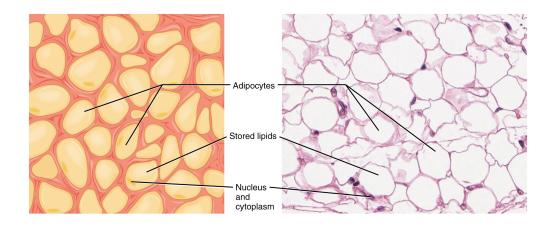
The macrophage cell is a large cell derived from a monocyte, a type of blood cell, which enters the connective tissue matrix from the blood vessels. The macrophage cells are an essential component of the immune system, which is the body's defense against potential pathogens and degraded host cells. When stimulated, macrophages release cytokines, small proteins that act as chemical messengers. Cytokines recruit other cells of the immune system to infected sites and stimulate their activities. Roaming, or free, macrophages move rapidly by amoeboid movement, engulfing infectious agents and cellular debris. In contrast, fixed macrophages are permanent residents of their tissues.

The mast cell, found in connective tissue proper, has many cytoplasmic granules. These granules contain the chemical signals histamine and heparin. When irritated or damaged, mast cells release histamine, an inflammatory mediator, which causes vasodilation and increased blood flow at a site of injury or infection, along with itching, swelling, and redness you recognize as an allergic response. Like blood cells, mast cells are derived from hematopoietic stem cells and are part of the immune system.

Loose Connective Tissue

Loose connective tissue is found between many organs where it acts both to absorb shock and bind tissues together. It allows water, salts, and various nutrients to diffuse through to adjacent or imbedded cells and tissues.

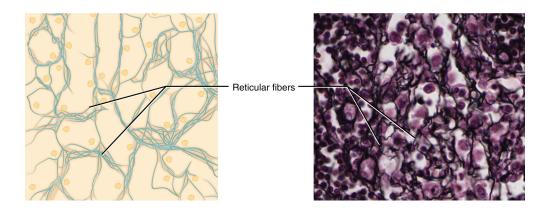
Adipose tissue consists mostly of fat storage cells, with little extracellular matrix ([link]). A large number of capillaries allow rapid storage and mobilization of lipid molecules. White adipose tissue is most abundant. It can appear yellow and owes its color to carotene and related pigments from plant food. White fat contributes mostly to lipid storage and can serve as insulation from cold temperatures and mechanical injuries. White adipose tissue can be found protecting the kidneys and cushioning the back of the eye. Brown adipose tissue is more common in infants, hence the term "baby fat." In adults, there is a reduced amount of brown fat and it is found mainly in the neck and clavicular regions of the body. The many mitochondria in the cytoplasm of brown adipose tissue help explain its efficiency at metabolizing stored fat. Brown adipose tissue is thermogenic, meaning that as it breaks down fats, it releases metabolic heat, rather than producing adenosine triphosphate (ATP), a key molecule used in metabolism. Adipose Tissue



This is a loose connective tissue that consists of fat cells with little extracellular matrix. It stores fat for energy and provides insulation. LM × 800. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Areolar tissue shows little specialization. It contains all the cell types and fibers previously described and is distributed in a random, web-like fashion. It fills the spaces between muscle fibers, surrounds blood and lymph vessels, and supports organs in the abdominal cavity. Areolar tissue underlies most epithelia and represents the connective tissue component of epithelial membranes, which are described further in a later section.

Reticular tissue is a mesh-like, supportive framework for soft organs such as lymphatic tissue, the spleen, and the liver ([link]). Reticular cells produce the reticular fibers that form the network onto which other cells attach. It derives its name from the Latin *reticulus*, which means "little net." Reticular Tissue



This is a loose connective tissue made up of a network of reticular fibers that provides a supportive framework for soft organs. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

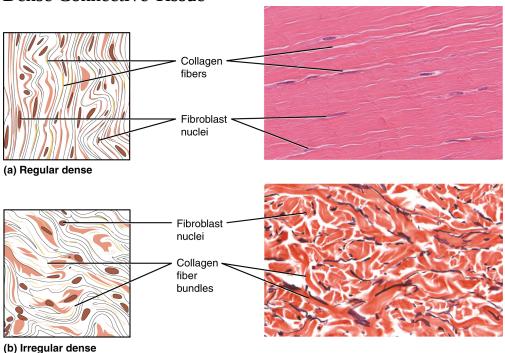
Dense Connective Tissue

Dense connective tissue contains more collagen fibers than does loose connective tissue. As a consequence, it displays greater resistance to stretching. There are two major categories of dense connective tissue: regular and irregular. Dense regular connective tissue fibers are parallel to each other, enhancing tensile strength and resistance to stretching in the direction of the fiber orientations. Ligaments and tendons are made of dense regular connective tissue, but in ligaments not all fibers are parallel. Dense regular elastic tissue contains elastin fibers in addition to collagen fibers, which allows the ligament to return to its original length after stretching. The ligaments in the vocal folds and between the vertebrae in the vertebral column are elastic.

In dense irregular connective tissue, the direction of fibers is random. This arrangement gives the tissue greater strength in all directions and less strength in one particular direction. In some tissues, fibers crisscross and form a mesh. In other tissues, stretching in several directions is achieved by

alternating layers where fibers run in the same orientation in each layer, and it is the layers themselves that are stacked at an angle. The dermis of the skin is an example of dense irregular connective tissue rich in collagen fibers. Dense irregular elastic tissues give arterial walls the strength and the ability to regain original shape after stretching ([link]).

Dense Connective Tissue



(a) Dense regular connective tissue consists of collagenous fibers packed into parallel bundles. (b) Dense irregular connective tissue consists of collagenous fibers interwoven into a mesh-like network. From top, LM × 1000, LM × 200. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

Note:

Disorders of the...

Connective Tissue: Tendinitis

Your opponent stands ready as you prepare to hit the serve, but you are confident that you will smash the ball past your opponent. As you toss the ball high in the air, a burning pain shoots across your wrist and you drop the tennis racket. That dull ache in the wrist that you ignored through the summer is now an unbearable pain. The game is over for now. After examining your swollen wrist, the doctor in the emergency room announces that you have developed wrist tendinitis. She recommends icing the tender area, taking non-steroidal anti-inflammatory medication to ease the pain and to reduce swelling, and complete rest for a few weeks. She interrupts your protests that you cannot stop playing. She issues a stern warning about the risk of aggravating the condition and the possibility of surgery. She consoles you by mentioning that well known tennis players such as Venus and Serena Williams and Rafael Nadal have also suffered from tendinitis related injuries.

What is tendinitis and how did it happen? Tendinitis is the inflammation of a tendon, the thick band of fibrous connective tissue that attaches a muscle to a bone. The condition causes pain and tenderness in the area around a joint. On rare occasions, a sudden serious injury will cause tendinitis. Most often, the condition results from repetitive motions over time that strain the tendons needed to perform the tasks.

Persons whose jobs and hobbies involve performing the same movements over and over again are often at the greatest risk of tendinitis. You hear of tennis and golfer's elbow, jumper's knee, and swimmer's shoulder. In all cases, overuse of the joint causes a microtrauma that initiates the inflammatory response. Tendinitis is routinely diagnosed through a clinical examination. In case of severe pain, X-rays can be examined to rule out the possibility of a bone injury. Severe cases of tendinitis can even tear loose a tendon. Surgical repair of a tendon is painful. Connective tissue in the tendon does not have abundant blood supply and heals slowly. While older adults are at risk for tendinitis because the elasticity of tendon tissue decreases with age, active people of all ages can develop tendinitis. Young athletes, dancers, and computer operators; anyone who performs the same movements constantly is at risk for tendinitis. Although repetitive motions are unavoidable in many activities and may lead to tendinitis, precautions can be taken that can lessen the probability of developing tendinitis. For active individuals, stretches before exercising and cross training or changing exercises are recommended. For the passionate

athlete, it may be time to take some lessons to improve technique. All of the preventive measures aim to increase the strength of the tendon and decrease the stress put on it. With proper rest and managed care, you will be back on the court to hit that slice-spin serve over the net.

Note:



Watch this <u>animation</u> to learn more about tendonitis, a painful condition caused by swollen or injured tendons.

Supportive Connective Tissues

Two major forms of supportive connective tissue, cartilage and bone, allow the body to maintain its posture and protect internal organs.

Cartilage

The distinctive appearance of cartilage is due to polysaccharides called chondroitin sulfates, which bind with ground substance proteins to form proteoglycans. Embedded within the cartilage matrix are **chondrocytes**, or cartilage cells, and the space they occupy are called **lacunae** (singular = lacuna). A layer of dense irregular connective tissue, the perichondrium, encapsulates the cartilage. Cartilaginous tissue is avascular, thus all nutrients need to diffuse through the matrix to reach the chondrocytes. This is a factor contributing to the very slow healing of cartilaginous tissues.

Bone

Bone is the hardest connective tissue. It provides protection to internal organs and supports the body. Bone's rigid extracellular matrix contains mostly collagen fibers embedded in a mineralized ground substance containing hydroxyapatite, a form of calcium phosphate. Both components of the matrix, organic and inorganic, contribute to the unusual properties of bone. Without collagen, bones would be brittle and shatter easily. Without mineral crystals, bones would flex and provide little support. Osteocytes, bone cells like chondrocytes, are located within lacunae. The histology of transverse tissue from long bone shows a typical arrangement of osteocytes in concentric circles around a central canal. Bone is a highly vascularized tissue. Unlike cartilage, bone tissue can recover from injuries in a relatively short time.

Cancellous bone looks like a sponge under the microscope and contains empty spaces between trabeculae, or arches of bone proper. It is lighter than compact bone and found in the interior of some bones and at the end of long bones. Compact bone is solid and has greater structural strength.

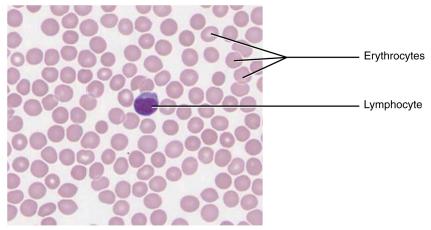
Fluid Connective Tissue

Blood and lymph are fluid connective tissues. Cells circulate in a liquid extracellular matrix. The formed elements circulating in blood are all derived from hematopoietic stem cells located in bone marrow ([link]). Erythrocytes, red blood cells, transport oxygen and some carbon dioxide. Leukocytes, white blood cells, are responsible for defending against potentially harmful microorganisms or molecules. Platelets are cell fragments involved in blood clotting. Some white blood cells have the ability to cross the endothelial layer that lines blood vessels and enter adjacent tissues. Nutrients, salts, and wastes are dissolved in the liquid matrix and transported through the body.

Lymph contains a liquid matrix and white blood cells. Lymphatic capillaries are extremely permeable, allowing larger molecules and excess fluid from interstitial spaces to enter the lymphatic vessels. Lymph drains into blood vessels, delivering molecules to the blood that could not otherwise directly

enter the bloodstream. In this way, specialized lymphatic capillaries transport absorbed fats away from the intestine and deliver these molecules to the blood.

Blood: A Fluid Connective Tissue



Blood is a fluid connective tissue containing erythrocytes and various types of leukocytes that circulate in a liquid extracellular matrix. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the University of Michigan Webscope at http://virtualslides.med.umich.edu/Histology/Cardiovascular%20System/0

<u>81-3 HISTO 40X.svs/view.apml</u> to explore the tissue sample in greater detail.

Note:



Visit this <u>link</u> to test your connective tissue knowledge with this 10-question quiz. Can you name the 10 tissue types shown in the histology slides?

Chapter Review

Connective tissue is a heterogeneous tissue with many cell shapes and tissue architecture. Structurally, all connective tissues contain cells that are embedded in an extracellular matrix stabilized by proteins. The chemical nature and physical layout of the extracellular matrix and proteins vary enormously among tissues, reflecting the variety of functions that connective tissue fulfills in the body. Connective tissues separate and cushion organs, protecting them from shifting or traumatic injury. Connect tissues provide support and assist movement, store and transport energy molecules, protect against infections, and contribute to temperature homeostasis.

Many different cells contribute to the formation of connective tissues. They originate in the mesodermal germ layer and differentiate from mesenchyme and hematopoietic tissue in the bone marrow. Fibroblasts are the most abundant and secrete many protein fibers, adipocytes specialize in fat storage, hematopoietic cells from the bone marrow give rise to all the blood cells, chondrocytes form cartilage, and osteocytes form bone. The

extracellular matrix contains fluid, proteins, polysaccharide derivatives, and, in the case of bone, mineral crystals. Protein fibers fall into three major groups: collagen fibers that are thick, strong, flexible, and resist stretch; reticular fibers that are thin and form a supportive mesh; and elastin fibers that are thin and elastic.

The major types of connective tissue are connective tissue proper, supportive tissue, and fluid tissue. Loose connective tissue proper includes adipose tissue, areolar tissue, and reticular tissue. These serve to hold organs and other tissues in place and, in the case of adipose tissue, isolate and store energy reserves. The matrix is the most abundant feature for loose tissue although adipose tissue does not have much extracellular matrix. Dense connective tissue proper is richer in fibers and may be regular, with fibers oriented in parallel as in ligaments and tendons, or irregular, with fibers oriented in several directions. Organ capsules (collagenous type) and walls of arteries (elastic type) contain dense irregular connective tissue. Cartilage and bone are supportive tissue. Cartilage contains chondrocytes and is somewhat flexible. Hyaline cartilage is smooth and clear, covers joints, and is found in the growing portion of bones. Fibrocartilage is tough because of extra collagen fibers and forms, among other things, the intervertebral discs. Elastic cartilage can stretch and recoil to its original shape because of its high content of elastic fibers. The matrix contains very few blood vessels. Bones are made of a rigid, mineralized matrix containing calcium salts, crystals, and osteocytes lodged in lacunae. Bone tissue is highly vascularized. Cancellous bone is spongy and less solid than compact bone. Fluid tissue, for example blood and lymph, is characterized by a liquid matrix and no supporting fibers.

Glossary

adipocytes lipid storage cells

adipose tissue specialized areolar tissue rich in stored fat

areolar tissue

(also, loose connective tissue) a type of connective tissue proper that shows little specialization with cells dispersed in the matrix

chondrocytes

cells of the cartilage

connective tissue proper

connective tissue containing a viscous matrix, fibers, and cells.

dense connective tissue

connective tissue proper that contains many fibers that provide both elasticity and protection

fibroblast

most abundant cell type in connective tissue, secretes protein fibers and matrix into the extracellular space

fibrocyte

less active form of fibroblast

fluid connective tissue

specialized cells that circulate in a watery fluid containing salts, nutrients, and dissolved proteins

ground substance

fluid or semi-fluid portion of the matrix

lacunae

(singular = lacuna) small spaces in bone or cartilage tissue that cells occupy

loose connective tissue

(also, areolar tissue) type of connective tissue proper that shows little specialization with cells dispersed in the matrix

matrix

extracellular material which is produced by the cells embedded in it, containing ground substance and fibers

mesenchymal cell

adult stem cell from which most connective tissue cells are derived

reticular tissue

type of loose connective tissue that provides a supportive framework to soft organs, such as lymphatic tissue, spleen, and the liver

supportive connective tissue

type of connective tissue that provides strength to the body and protects soft tissue

OU Human Physiology: Muscle Tissue and Motion By the end of this section, you will be able to:

- Identify the three types of muscle tissue
- Compare and contrast the functions of each muscle tissue type
- Explain how muscle tissue can enable motion

Muscle tissue is characterized by properties that allow movement. Muscle cells are excitable; they respond to a stimulus. They are contractile, meaning they can shorten and generate a pulling force. When attached between two movable objects, in other words, bones, contractions of the muscles cause the bones to move. Some muscle movement is voluntary, which means it is under conscious control. For example, a person decides to open a book and read a chapter on anatomy. Other movements are involuntary, meaning they are not under conscious control, such as the contraction of your pupil in bright light. Muscle tissue is classified into three types according to structure and function: skeletal, cardiac, and smooth ([link]).

Comparison of Structure and Properties of Muscle Tissue Types					
Tissue	Histology	Function	Location		
Skeletal	Long cylindrical fiber, striated, many peripherally located nuclei	Voluntary movement, produces heat, protects organs	Attached to bones and around entrance points to body (e.g., mouth, anus)		

Comparison of Structure and Properties of Muscle Tissue Types				
Tissue	Histology	Function	Location	
Cardiac	Short, branched, striated, single central nucleus	Contracts to pump blood	Heart	
Smooth	Short, spindle- shaped, no evident striation, single nucleus in each fiber	Involuntary movement, moves food, involuntary control of respiration, moves secretions, regulates flow of blood in arteries by contraction	Walls of major organs and passageways	

Skeletal muscle is attached to bones and its contraction makes possible locomotion, facial expressions, posture, and other voluntary movements of the body. Forty percent of your body mass is made up of skeletal muscle. Skeletal muscles generate heat as a byproduct of their contraction and thus participate in thermal homeostasis. Shivering is an involuntary contraction of skeletal muscles in response to perceived lower than normal body temperature. The muscle cell, or **myocyte**, develops from myoblasts derived from the mesoderm. Myocytes and their numbers remain relatively constant throughout life. Skeletal muscle tissue is arranged in bundles surrounded by connective tissue. Under the light microscope, muscle cells appear striated with many nuclei squeezed along the membranes. The **striation** is due to the regular alternation of the contractile proteins actin and myosin, along with the structural proteins that couple the contractile proteins to connective tissues. The cells are multinucleated as a result of the fusion of the many myoblasts that fuse to form each long muscle fiber.

Cardiac muscle forms the contractile walls of the heart. The cells of cardiac muscle, known as cardiomyocytes, also appear striated under the microscope. Unlike skeletal muscle fibers, cardiomyocytes are single cells typically with a single centrally located nucleus. A principal characteristic of cardiomyocytes is that they contract on their own intrinsic rhythms without any external stimulation. Cardiomyocyte attach to one another with specialized cell junctions called intercalated discs. Intercalated discs have both anchoring junctions and gap junctions. Attached cells form long, branching cardiac muscle fibers that are, essentially, a mechanical and electrochemical syncytium allowing the cells to synchronize their actions. The cardiac muscle pumps blood through the body and is under involuntary control. The attachment junctions hold adjacent cells together across the dynamic pressures changes of the cardiac cycle.

Smooth muscle tissue contraction is responsible for involuntary movements in the internal organs. It forms the contractile component of the digestive, urinary, and reproductive systems as well as the airways and arteries. Each cell is spindle shaped with a single nucleus and no visible striations ([link]).

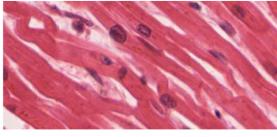
Muscle Tissue



(a)



(b)



(c)

(a) Skeletal muscle cells have prominent striation and nuclei on their periphery. (b) Smooth muscle cells have a single nucleus and no visible striations. (c) Cardiac muscle cells appear striated and have a single nucleus. From top, LM × 1600, LM × 1600, LM × 1600. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

Note:



Watch this <u>video</u> to learn more about muscle tissue. In looking through a microscope how could you distinguish skeletal muscle tissue from smooth muscle?

Chapter Review

The three types of muscle cells are skeletal, cardiac, and smooth. Their morphologies match their specific functions in the body. Skeletal muscle is voluntary and responds to conscious stimuli. The cells are striated and multinucleated appearing as long, unbranched cylinders. Cardiac muscle is involuntary and found only in the heart. Each cell is striated with a single nucleus and they attach to one another to form long fibers. Cells are attached to one another at intercalated disks. The cells are interconnected physically and electrochemically to act as a syncytium. Cardiac muscle cells contract autonomously and involuntarily. Smooth muscle is involuntary. Each cell is a spindle-shaped fiber and contains a single nucleus. No striations are evident because the actin and myosin filaments do not align in the cytoplasm.

Glossary

cardiac muscle

heart muscle, under involuntary control, composed of striated cells that attach to form fibers, each cell contains a single nucleus, contracts autonomously

myocyte

muscle cells

skeletal muscle

usually attached to bone, under voluntary control, each cell is a fiber that is multinucleated and striated

smooth muscle

under involuntary control, moves internal organs, cells contain a single nucleus, are spindle-shaped, and do not appear striated; each cell is a fiber

striation

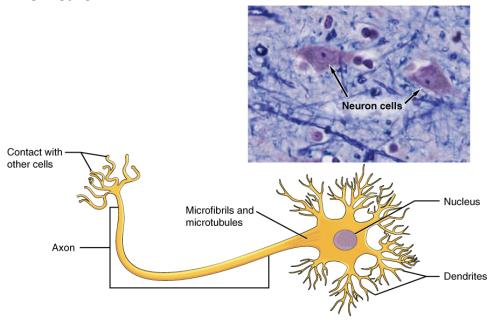
alignment of parallel actin and myosin filaments which form a banded pattern

OU Human Physiology: Nervous Tissue Mediates Perception and Response By the end of this section, you will be able to:

- Identify the classes of cells that make up nervous tissue
- Discuss how nervous tissue mediates perception and response

Nervous tissue is characterized as being excitable and capable of sending and receiving electrochemical signals that provide the body with information. Two main classes of cells make up nervous tissue: the **neuron** and **neuroglia** ([link]). Neurons propagate information via electrochemical impulses, called action potentials, which are biochemically linked to the release of chemical signals. Neuroglia play an essential role in supporting neurons and modulating their information propagation.

The Neuron



The cell body of a neuron, also called the soma, contains the nucleus and mitochondria. The dendrites transfer the nerve impulse to the soma. The axon carries the action potential away to another excitable cell. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



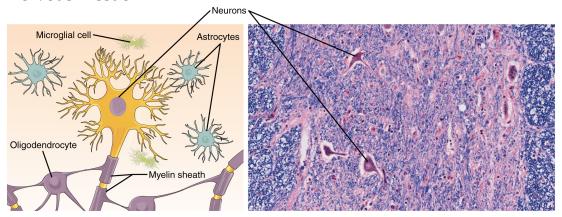
Follow this <u>link</u> to learn more about nervous tissue. What are the main parts of a nerve cell?

Neurons display distinctive morphology, well suited to their role as conducting cells, with three main parts. The cell body includes most of the cytoplasm, the organelles, and the nucleus. Dendrites branch off the cell body and appear as thin extensions. A long "tail," the axon, extends from the neuron body and can be wrapped in an insulating layer known as **myelin**, which is formed by accessory cells. The synapse is the gap between nerve cells, or between a nerve cell and its target, for example, a muscle or a gland, across which the impulse is transmitted by chemical compounds known as neurotransmitters. Neurons categorized as multipolar neurons have several dendrites and a single prominent axon. Bipolar neurons possess a single dendrite and axon with the cell body, while unipolar neurons have only a single process extending out from the cell body, which divides into a functional dendrite and into a functional axon. When a neuron is sufficiently stimulated, it generates an action potential that propagates down the axon towards the synapse. If enough neurotransmitters are released at the synapse to stimulate the next neuron or target, a response is generated.

The second class of neural cells comprises the neuroglia or glial cells, which have been characterized as having a simple support role. The word "glia" comes from the Greek word for glue. Recent research is shedding light on the more complex role of neuroglia in the function of the brain and nervous system. **Astrocyte** cells, named for their distinctive star shape, are abundant in the central nervous system. The astrocytes have many

functions, including regulation of ion concentration in the intercellular space, uptake and/or breakdown of some neurotransmitters, and formation of the blood-brain barrier, the membrane that separates the circulatory system from the brain. Microglia protect the nervous system against infection but are not nervous tissue because they are related to macrophages. **Oligodendrocyte** cells produce myelin in the central nervous system (brain and spinal cord) while the **Schwann cell** produces myelin in the peripheral nervous system ([link]).

Nervous Tissue



Nervous tissue is made up of neurons and neuroglia. The cells of nervous tissue are specialized to transmit and receive impulses. LM × 872. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

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Chapter Review

The most prominent cell of the nervous tissue, the neuron, is characterized mainly by its ability to receive stimuli and respond by generating an electrical signal, known as an action potential, which can travel rapidly over great distances in the body. A typical neuron displays a distinctive morphology: a large cell body branches out into short extensions called dendrites, which receive chemical signals from other neurons, and a long tail called an axon, which relays signals away from the cell to other neurons, muscles, or glands. Many axons are wrapped by a myelin sheath, a lipid derivative that acts as an insulator and speeds up the transmission of the action potential. Other cells in the nervous tissue, the neuroglia, include the astrocytes, microglia, oligodendrocytes, and Schwann cells.

Glossary

astrocyte

star-shaped cell in the central nervous system that regulates ions and uptake and/or breakdown of some neurotransmitters and contributes to the formation of the blood-brain barrier

myelin

layer of lipid inside some neuroglial cells that wraps around the axons of some neurons

neuroglia

supportive neural cells

neuron

excitable neural cell that transfer nerve impulses

oligodendrocyte

neuroglial cell that produces myelin in the brain

Schwann cell

neuroglial cell that produces myelin in the peripheral nervous system

OU Human Physiology: Introduction to Biomolecules

Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Compare and contrast the four important classes of organic compounds – carbohydrates, lipids, proteins, and nucleic acids – according to their composition and functional importance to human life
- Describe the structure and function of the cellular organelles
- Integrate and synthesize chemistry knowledge of macromolecules to functions of cellular organelles
- Explain the structure and function of DNA
- Describe the purpose of DNA replication
- Compare and contrast transcription and translation in protein synthesis
- Describe the importance of cell division and its regulation
- Describe how a cell differentiates and becomes more specialized
- Distinguish between the categories of stem cells

Human chemistry includes organic molecules (carbon-based) and biomolecules (those produced by the body). Human chemistry also includes elements. In fact, life cannot exist without many of the elements that are part of the earth. All of the elements that contribute to chemical reactions, to the transformation of energy, and to electrical activity and muscle contraction—elements that include phosphorus, carbon, sodium, and calcium, to name a few—originated in stars. These elements, in turn, can form both the inorganic and organic chemical compounds important to life, including, for example, water, glucose, and proteins. For a review of inorganic chemistry please read the "Chemistry Refresher" as this chapter will begin with organic chemistry, specifically, those molecules that contain carbon and are essential to life. These are the biomolecules and include

proteins, lipids, carbohydrates, and nucleotides. Once this framework is set, this chapter will move on to cells, the fundamental unit of life.

OU Human Physiology: Organic Compounds Essential to Human Functioning

By the end of this section, you will be able to:

- Identify four types of organic molecules essential to human functioning
- Explain the chemistry behind carbon's affinity for covalently bonding in organic compounds
- Provide examples of three types of carbohydrates, and identify the primary functions of carbohydrates in the body
- Discuss four types of lipids important in human functioning
- Describe the structure of proteins, and discuss their importance to human functioning
- Identify the building blocks of nucleic acids, and the roles of DNA, RNA, and ATP in human functioning

Organic compounds typically consist of groups of carbon atoms covalently bonded to hydrogen, usually oxygen, and often other elements as well. Created by living things, they are found throughout the world, in soils and seas, commercial products, and every cell of the human body. The four types most important to human structure and function are carbohydrates, lipids, proteins, and nucleotides. Before exploring these compounds, you need to first understand the chemistry of carbon.

The Chemistry of Carbon

What makes organic compounds ubiquitous is the chemistry of their carbon core. Recall that carbon atoms have four electrons in their valence shell, and that the octet rule dictates that atoms tend to react in such a way as to complete their valence shell with eight electrons. Carbon atoms do not complete their valence shells by donating or accepting four electrons. Instead, they readily share electrons via covalent bonds.

Commonly, carbon atoms share with other carbon atoms, often forming a long carbon chain referred to as a carbon skeleton. When they do share, however, they do not share all their electrons exclusively with each other. Rather, carbon atoms tend to share electrons with a variety of other

elements, one of which is always hydrogen. Carbon and hydrogen groupings are called hydrocarbons. If you study the figures of organic compounds in the remainder of this chapter, you will see several with chains of hydrocarbons in one region of the compound.

Many combinations are possible to fill carbon's four "vacancies." Carbon may share electrons with oxygen or nitrogen or other atoms in a particular region of an organic compound. Moreover, the atoms to which carbon atoms bond may also be part of a functional group. A **functional group** is a group of atoms linked by strong covalent bonds and tending to function in chemical reactions as a single unit. You can think of functional groups as tightly knit "cliques" whose members are unlikely to be parted. Five functional groups are important in human physiology; these are the hydroxyl, carboxyl, amino, methyl and phosphate groups ([link]).

Functional Groups Important in Human Physiology				
Functional group	Structural formula	Importance		
Hydroxyl	—О—Н	Hydroxyl groups are polar. They are components of all four types of organic compounds discussed in this chapter. They are involved in dehydration synthesis and hydrolysis reactions.		
Carboxyl	O—C— OH	Carboxyl groups are found within fatty acids, amino acids, and many other acids.		

Functional Groups Important in Human Physiology			
Functional group	Structural formula	Importance	
Amino	—N—H ₂	Amino groups are found within amino acids, the building blocks of proteins.	
Methyl	—C—H ₃	Methyl groups are found within amino acids.	
Phosphate	—P—O ₄ ²⁻	Phosphate groups are found within phospholipids and nucleotides.	

Carbon's affinity for covalent bonding means that many distinct and relatively stable organic molecules nevertheless readily form larger, more complex molecules. Any large molecule is referred to as **macromolecule** (macro-= "large"), and the organic compounds in this section all fit this description. However, some macromolecules are made up of several "copies" of single units called monomer (mono-= "one"; -mer = "part"). Like beads in a long necklace, these monomers link by covalent bonds to form long polymers (poly-= "many"). There are many examples of monomers and polymers among the organic compounds.

Monomers form polymers by engaging in dehydration synthesis (see [link]). As was noted earlier, this reaction results in the release of a molecule of water. Each monomer contributes: One gives up a hydrogen atom and the other gives up a hydroxyl group. Polymers are split into monomers by hydrolysis (-lysis = "rupture"). The bonds between their monomers are broken, via the donation of a molecule of water, which contributes a hydrogen atom to one monomer and a hydroxyl group to the other.

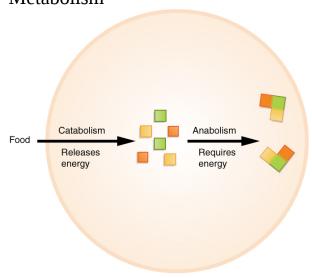
Metabolic Reactions

The first law of thermodynamics holds that energy can neither be created nor destroyed—it can only change form. Your basic function as an organism is to consume (ingest) energy and molecules in the foods you eat, convert some of it into fuel for movement, sustain your body functions, and build and maintain your body structures. There are two types of reactions that accomplish this: **anabolism** and **catabolism**.

- **Anabolism** is the process whereby smaller, simpler molecules are combined into larger, more complex substances. Your body can assemble, by utilizing energy, the complex chemicals it needs by combining small molecules derived from the foods you eat
- **Catabolism** is the process by which larger more complex substances are broken down into smaller simpler molecules. Catabolism releases energy. The complex molecules found in foods are broken down so the body can use their parts to assemble the structures and substances needed for life.

Taken together, these two processes are called metabolism. **Metabolism** is the sum of all anabolic and catabolic reactions that take place in the body ([link]). Both anabolism and catabolism occur simultaneously and continuously to keep you alive.

Metabolism



Anabolic reactions are building reactions, and they consume energy. Catabolic reactions

break materials down and release energy. Metabolism includes both anabolic and catabolic reactions.

Every cell in your body makes use of a chemical compound, **adenosine triphosphate** (ATP), to store and release energy. The cell stores energy in the synthesis (anabolism) of ATP, then moves the ATP molecules to the location where energy is needed to fuel cellular activities. Then the ATP is broken down (catabolism) and a controlled amount of energy is released, which is used by the cell to perform a particular job.

Carbohydrates

The term carbohydrate means "hydrated carbon." Recall that the root hydro- indicates water. A **carbohydrate** is a molecule composed of carbon, hydrogen, and oxygen; in most carbohydrates, hydrogen and oxygen are found in the same two-to-one relative proportions they have in water. In fact, the chemical formula for a "generic" molecule of carbohydrate is $(CH_2O)_n$.

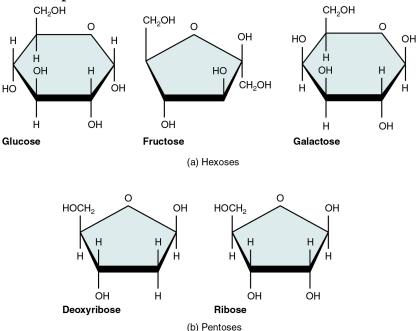
Carbohydrates are referred to as saccharides, a word meaning "sugars." Three forms are important in the body. Monosaccharides are the monomers of carbohydrates. Disaccharides (di- = "two") are made up of two monomers. **Polysaccharides** are the polymers, and can consist of hundreds to thousands of monomers.

Monosaccharides

A **monosaccharide** is a monomer of carbohydrates. Five monosaccharides are important in the body. Three of these are the hexose sugars, so called because they each contain six atoms of carbon. These are glucose, fructose, and galactose, shown in [link]a. The remaining monosaccharides are the

two pentose sugars, each of which contains five atoms of carbon. They are ribose and deoxyribose, shown in [link]b.

Five Important Monosaccharides

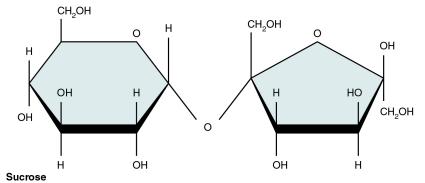


Disaccharides

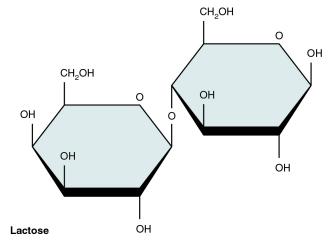
A **disaccharide** is a pair of monosaccharides. Disaccharides are formed via dehydration synthesis, and the bond linking them is referred to as a glycosidic bond (glyco-= "sugar"). Three disaccharides (shown in [link]) are important to humans. These are sucrose, commonly referred to as table sugar; lactose, or milk sugar; and maltose, or malt sugar. As you can tell from their common names, you consume these in your diet; however, your body cannot use them directly. Instead, in the digestive tract, they are split into their component monosaccharides via hydrolysis.

Three Important Disaccharides

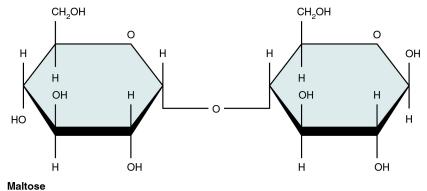
(a) The monosaccharides glucose and fructose bond to form sucrose



(b) The monosaccharides galactose and glucose bond to form lactose.



(c) Two glucose monosaccharides bond to form maltose.



All three important disaccharides form by dehydration synthesis.

Note:



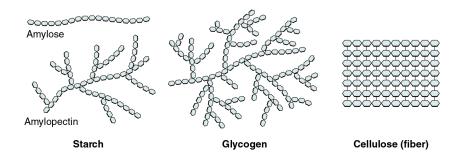
Watch this <u>video</u> to observe the formation of a disaccharide. What happens when water encounters a glycosidic bond?

Polysaccharides

Polysaccharides can contain a few to a thousand or more monosaccharides. Three are important to the body ([link]):

- Starches are polymers of glucose. They occur in long chains called amylose or branched chains called amylopectin, both of which are stored in plant-based foods and are relatively easy to digest.
- Glycogen is also a polymer of glucose, but it is stored in the tissues of animals, especially in the muscles and liver. It is not considered a dietary carbohydrate because very little glycogen remains in animal tissues after slaughter; however, the human body stores excess glucose as glycogen, again, in the muscles and liver.
- Cellulose, a polysaccharide that is the primary component of the cell wall of green plants, is the component of plant food referred to as "fiber". In humans, cellulose/fiber is not digestible; however, dietary fiber has many health benefits. It helps you feel full so you eat less, it promotes a healthy digestive tract, and a diet high in fiber is thought to reduce the risk of heart disease and possibly some forms of cancer.

Three Important Polysaccharides



Three important polysaccharides are starches, glycogen, and fiber.

Functions of Carbohydrates

The body obtains carbohydrates from plant-based foods. Grains, fruits, and legumes and other vegetables provide most of the carbohydrate in the human diet, although lactose is found in dairy products.

Although most body cells can break down other organic compounds for fuel, all body cells can use glucose. Moreover, nerve cells (neurons) in the brain, spinal cord, and through the peripheral nervous system, as well as red blood cells, can use only glucose for fuel. In the breakdown of glucose for energy, molecules of adenosine triphosphate, better known as ATP, are produced. **Adenosine triphosphate (ATP)** is composed of a ribose sugar, an adenine base, and three phosphate groups. ATP releases free energy when its phosphate bonds are broken, and thus supplies ready energy to the cell. More ATP is produced in the presence of oxygen (O_2) than in pathways that do not use oxygen. The overall reaction for the conversion of the energy in glucose to energy stored in ATP can be written:

Equation:

$$C_6H_{12}O_6 + 6 O_2 \rightarrow 6 CO_2 + 6 H_2O + ATP$$

In addition to being a critical fuel source, carbohydrates are present in very small amounts in cells' structure. For instance, some carbohydrate

molecules bind with proteins to produce glycoproteins, and others combine with lipids to produce glycolipids, both of which are found in the membrane that encloses the contents of body cells.

Lipids

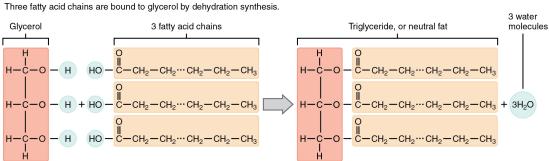
A **lipid** is one of a highly diverse group of compounds made up mostly of hydrocarbons. The few oxygen atoms they contain are often at the periphery of the molecule. Their nonpolar hydrocarbons make all lipids hydrophobic. In water, lipids do not form a true solution, but they may form an emulsion, which is the term for a mixture of solutions that do not mix well.

Triglycerides

A **triglyceride** is one of the most common dietary lipid groups, and the type found most abundantly in body tissues. This compound, which is commonly referred to as a fat, is formed from the synthesis of two types of molecules ([link]):

- A glycerol backbone at the core of triglycerides, consists of three carbon atoms.
- Three fatty acids, long chains of hydrocarbons with a carboxyl group and a methyl group at opposite ends, extend from each of the carbons of the glycerol.

Triglycerides

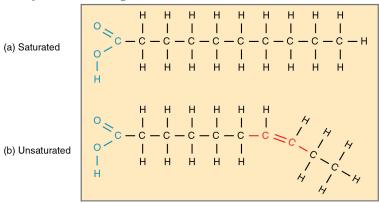


Triglycerides are composed of glycerol attached to three fatty acids via dehydration synthesis. Notice that glycerol gives up a hydrogen atom, and the carboxyl groups on the fatty acids each give up a hydroxyl group.

Triglycerides form via dehydration synthesis. Glycerol gives up hydrogen atoms from its hydroxyl groups at each bond, and the carboxyl group on each fatty acid chain gives up a hydroxyl group. A total of three water molecules are thereby released.

Fatty acid chains that have no double carbon bonds anywhere along their length and therefore contain the maximum number of hydrogen atoms are called saturated fatty acids. These straight, rigid chains pack tightly together and are solid or semi-solid at room temperature ([link]a). Butter and lard are examples, as is the fat found on a steak or in your own body. In contrast, fatty acids with one double carbon bond are kinked at that bond ([link]b). These monounsaturated fatty acids are therefore unable to pack together tightly, and are liquid at room temperature. Polyunsaturated fatty acids contain two or more double carbon bonds, and are also liquid at room temperature. Plant oils such as olive oil typically contain both mono- and polyunsaturated fatty acids.

Fatty Acid Shapes



The level of saturation of a fatty acid affects its shape. (a) Saturated fatty acid

chains are straight. (b) Unsaturated fatty acid chains are kinked.

Whereas a diet high in saturated fatty acids increases the risk of heart disease, a diet high in unsaturated fatty acids is thought to reduce the risk. This is especially true for the omega-3 unsaturated fatty acids found in cold-water fish such as salmon. These fatty acids have their first double carbon bond at the third hydrocarbon from the methyl group (referred to as the omega end of the molecule).

Finally, *trans* fatty acids found in some processed foods, including some stick and tub margarines, are thought to be even more harmful to the heart and blood vessels than saturated fatty acids. *Trans* fats are created from unsaturated fatty acids (such as corn oil) when chemically treated to produce partially hydrogenated fats.

As a group, triglycerides are a major fuel source for the body. When you are resting or asleep, a majority of the energy used to keep you alive is derived from triglycerides stored in your fat (adipose) tissues. Triglycerides also fuel long, slow physical activity such as gardening or hiking, and contribute a modest percentage of energy for vigorous physical activity. Dietary fat also assists the absorption and transport of the nonpolar fat-soluble vitamins A, D, E, and K. Additionally, stored body fat protects and cushions the body's bones and internal organs, and acts as insulation to retain body heat.

Fatty acids are also components of glycolipids, which are sugar-fat compounds found in the cell membrane. Lipoproteins are compounds in which the hydrophobic triglycerides are packaged in protein envelopes for transport in body fluids.

Phospholipids

As its name suggests, a **phospholipid** is a bond between the glycerol component of a lipid and a phosphorous molecule. In fact, phospholipids are similar in structure to triglycerides. However, instead of having three

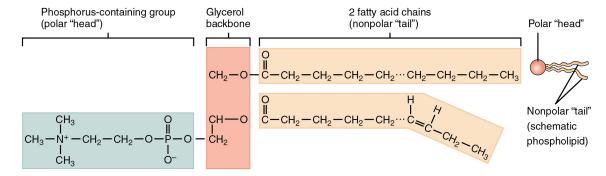
fatty acids, a phospholipid is generated from a diglyceride, a glycerol with just two fatty acid chains ([link]). The third binding site on the glycerol is taken up by the phosphate group, which in turn is attached to a polar "head" region of the molecule. Recall that triglycerides are nonpolar and hydrophobic. This still holds for the fatty acid portion of a phospholipid compound. However, the phosphate-containing group at the head of the compound is polar and thereby hydrophilic. In other words, one end of the molecule can interact with oil, and the other end with water. This makes phospholipids ideal emulsifiers, compounds that help disperse fats in aqueous liquids, and enables them to interact with both the watery interior of cells and the watery solution outside of cells as components of the cell membrane.

Other Important Lipids

(a) Phospholipids

Two fatty acid chains and a phosphorus-containing group are attached to the glycerol backbone.

Example: Phosphatidylcholine



(b) Sterols

Four interlocking hydrocarbon rings from a steroid.

Example: Cholesterol (cholesterol is the basis for all steroids formed in the body)

(c) Prostaglandins

(a) Phospholipids are composed of two fatty acids, glycerol, and a phosphate group. (b) Sterols are ring-shaped lipids. Shown here is cholesterol. (c) Prostaglandins are derived from unsaturated fatty acids. Prostaglandin E2 (PGE2) includes hydroxyl and carboxyl groups.

Steroids

A **steroid** compound (referred to as a sterol) has as its foundation a set of four hydrocarbon rings bonded to a variety of other atoms and molecules (see [link]b). Although both plants and animals synthesize sterols, the type that makes the most important contribution to human structure and function is cholesterol, which is synthesized by the liver in humans and animals and is also present in most animal-based foods. Like other lipids, cholesterol's hydrocarbons make it hydrophobic; however, it has a polar hydroxyl head that is hydrophilic. Cholesterol is an important component of bile acids, compounds that help emulsify dietary fats. In fact, the word root cholerefers to bile. Cholesterol is also a building block of many hormones, signaling molecules that the body releases to regulate processes at distant sites. Finally, like phospholipids, cholesterol molecules are found in the cell membrane, where their hydrophobic and hydrophilic regions help regulate the flow of substances into and out of the cell.

Prostaglandins

Like a hormone, a **prostaglandin** is one of a group of signaling molecules, but prostaglandins are derived from unsaturated fatty acids (see [link]c). One reason that the omega-3 fatty acids found in fish are beneficial is that they stimulate the production of certain prostaglandins that help regulate aspects of blood pressure and inflammation, and thereby reduce the risk for heart disease. Prostaglandins also sensitize nerves to pain. One class of pain-relieving medications called nonsteroidal anti-inflammatory drugs (NSAIDs) works by reducing the effects of prostaglandins.

Proteins

You might associate proteins with muscle tissue, but in fact, proteins are critical components of all tissues and organs. A **protein** is an organic molecule composed of amino acids linked by peptide bonds. Proteins include the keratin in the epidermis of skin that protects underlying tissues, the collagen found in the dermis of skin, in bones, and in the meninges that

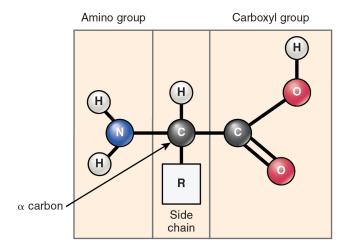
cover the brain and spinal cord. Proteins are also components of many of the body's functional chemicals, including digestive enzymes in the digestive tract, antibodies, the neurotransmitters that neurons use to communicate with other cells, and the peptide-based hormones that regulate certain body functions (for instance, growth hormone). While carbohydrates and lipids are composed of hydrocarbons and oxygen, all proteins also contain nitrogen (N), and many contain sulfur (S), in addition to carbon, hydrogen, and oxygen.

Microstructure of Proteins

Proteins are polymers made up of nitrogen-containing monomers called amino acids. An **amino acid** is a molecule composed of an amino group and a carboxyl group, together with a variable side chain. Just 20 different amino acids contribute to nearly all of the thousands of different proteins important in human structure and function. Body proteins contain a unique combination of a few dozen to a few hundred of these 20 amino acid monomers. All 20 of these amino acids share a similar structure ([link]). All consist of a central carbon atom to which the following are bonded:

- a hydrogen atom
- an alkaline (basic) amino group NH₂ (see [link])
- an acidic carboxyl group COOH (see [link])
- a variable group

Structure of an Amino Acid



Notice that all amino acids contain both an acid (the carboxyl group) and a base (the amino group) (amine = "nitrogen-containing"). For this reason, they make excellent buffers, helping the body regulate acid—base balance. What distinguishes the 20 amino acids from one another is their variable group, which is referred to as a side chain or an R-group. This group can vary in size and can be polar or nonpolar, giving each amino acid its unique characteristics. For example, the side chains of two amino acids—cysteine and methionine—contain sulfur. Sulfur does not readily participate in hydrogen bonds, whereas all other amino acids do. This variation influences the way that proteins containing cysteine and methionine are assembled.

Amino acids join via dehydration synthesis to form protein polymers ([link]). The unique bond holding amino acids together is called a peptide bond. A **peptide bond** is a covalent bond between two amino acids that forms by dehydration synthesis. A peptide, in fact, is a very short chain of amino acids. Strands containing fewer than about 100 amino acids are generally referred to as polypeptides rather than proteins.

Peptide Bond

Different amino acids join together to form peptides, polypeptides, or proteins via dehydration synthesis. The bonds between the amino acids are peptide bonds.

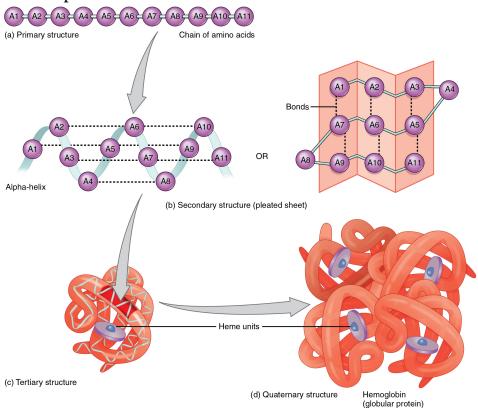
The body is able to synthesize most of the amino acids from components of other molecules; however, nine cannot be synthesized and have to be consumed in the diet. These are known as the essential amino acids.

Free amino acids available for protein construction are said to reside in the amino acid pool within cells. Structures within cells use these amino acids when assembling proteins. If a particular essential amino acid is not available in sufficient quantities in the amino acid pool, however, synthesis of proteins containing it can slow or even cease.

Shape of Proteins

Just as a fork cannot be used to eat soup and a spoon cannot be used to spear meat, a protein's shape is essential to its function. A protein's shape is determined, most fundamentally, by the sequence of amino acids of which it is made ([link]a). The sequence is called the primary structure of the protein.

The Shape of Proteins



(a) The primary structure is the sequence of amino acids that make up the polypeptide chain. (b) The secondary structure, which can take the form of an alpha-helix or a beta-pleated sheet, is maintained by hydrogen bonds between amino acids in different regions of the original polypeptide strand. (c) The tertiary structure occurs as a result of further folding and bonding of the secondary structure. (d) The quaternary structure occurs as a result of interactions between two or more tertiary subunits. The example shown here is hemoglobin, a protein in red blood cells which transports oxygen to body tissues.

Although some polypeptides exist as linear chains, most are twisted or folded into more complex secondary structures that form when bonding

occurs between amino acids with different properties at different regions of the polypeptide. The most common secondary structure is a spiral called an alpha-helix. If you were to take a length of string and simply twist it into a spiral, it would not hold the shape. Similarly, a strand of amino acids could not maintain a stable spiral shape without the help of hydrogen bonds, which create bridges between different regions of the same strand (see [link]b). Less commonly, a polypeptide chain can form a beta-pleated sheet, in which hydrogen bonds form bridges between different regions of a single polypeptide that has folded back upon itself, or between two or more adjacent polypeptide chains.

The secondary structure of proteins further folds into a compact three-dimensional shape, referred to as the protein's tertiary structure (see [link]c). In this configuration, amino acids that had been very distant in the primary chain can be brought quite close via hydrogen bonds or, in proteins containing cysteine, via disulfide bonds. A **disulfide bond** is a covalent bond between sulfur atoms in a polypeptide. Often, two or more separate polypeptides bond to form an even larger protein with a quaternary structure (see [link]d). The polypeptide subunits forming a quaternary structure can be identical or different. For instance, hemoglobin, the protein found in red blood cells is composed of four tertiary polypeptides, two of which are called alpha chains and two of which are called beta chains.

When they are exposed to extreme heat, acids, bases, and certain other substances, proteins will denature. **Denaturation** is a change in the structure of a molecule through physical or chemical means. Denatured proteins lose their functional shape and are no longer able to carry out their jobs. An everyday example of protein denaturation is the curdling of milk when acidic lemon juice is added.

The contribution of the shape of a protein to its function can hardly be exaggerated. For example, the long, slender shape of protein strands that make up muscle tissue is essential to their ability to contract (shorten) and relax (lengthen). As another example, bones contain long threads of a protein called collagen that acts as scaffolding upon which bone minerals are deposited. These elongated proteins, called fibrous proteins, are strong and durable and typically hydrophobic.

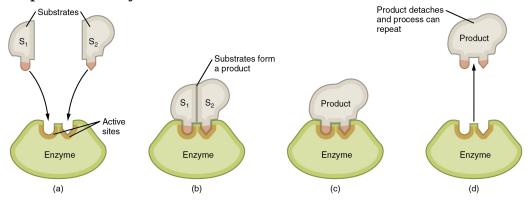
In contrast, globular proteins are globes or spheres that tend to be highly reactive and are hydrophilic. The hemoglobin proteins packed into red blood cells are an example (see [link]d); however, globular proteins are abundant throughout the body, playing critical roles in most body functions. Enzymes, introduced earlier as protein catalysts, are examples of this. The next section takes a closer look at the action of enzymes.

Proteins Function as Enzymes

If you were trying to type a paper, and every time you hit a key on your laptop there was a delay of six or seven minutes before you got a response, you would probably get a new laptop. In a similar way, without enzymes to catalyze chemical reactions, the human body would be nonfunctional. It functions only because enzymes function.

Enzymatic reactions—chemical reactions catalyzed by enzymes—begin when substrates bind to the enzyme. A **substrate** is a reactant in an enzymatic reaction. This occurs on regions of the enzyme known as active sites ([link]). Any given enzyme catalyzes just one type of chemical reaction. This characteristic, called specificity, is due to the fact that a substrate with a particular shape and electrical charge can bind only to an active site corresponding to that substrate.

Steps in an Enzymatic Reaction



(a) Substrates approach active sites on enzyme. (b) Substrates bind to active sites, producing an enzyme—substrate complex. (c) Changes internal to the enzyme—

substrate complex facilitate interaction of the substrates. (d) Products are released and the enzyme returns to its original form, ready to facilitate another enzymatic reaction.

Binding of a substrate produces an enzyme—substrate complex. It is likely that enzymes speed up chemical reactions in part because the enzyme—substrate complex undergoes a set of temporary and reversible changes that cause the substrates to be oriented toward each other in an optimal position to facilitate their interaction. This promotes increased reaction speed. The enzyme then releases the product(s), and resumes its original shape. The enzyme is then free to engage in the process again, and will do so as long as substrate remains.

Other Functions of Proteins

Advertisements for protein bars, powders, and shakes all say that protein is important in building, repairing, and maintaining muscle tissue, but the truth is that proteins contribute to all body tissues, from the skin to the brain cells. Also, certain proteins act as hormones, chemical messengers that help regulate body functions, For example, growth hormone is important for skeletal growth, among other roles.

As was noted earlier, the basic and acidic components enable proteins to function as buffers in maintaining acid—base balance, but they also help regulate fluid—electrolyte balance. Proteins attract fluid, and a healthy concentration of proteins in the blood, the cells, and the spaces between cells helps ensure a balance of fluids in these various "compartments." Moreover, proteins in the cell membrane help to transport electrolytes in and out of the cell, keeping these ions in a healthy balance. Like lipids, proteins can bind with carbohydrates. They can thereby produce glycoproteins or proteoglycans, both of which have many functions in the body.

The body can use proteins for energy when carbohydrate and fat intake is inadequate, and stores of glycogen and adipose tissue become depleted. However, since there is no storage site for protein except functional tissues, using protein for energy causes tissue breakdown, and results in body wasting.

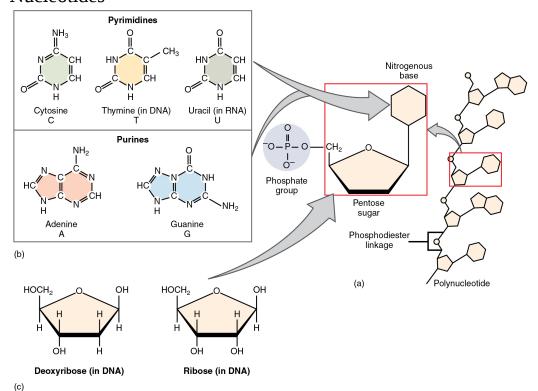
Nucleotides

The fourth type of organic compound important to human structure and function are the nucleotides ([link]). A **nucleotide** is one of a class of organic compounds composed of three subunits:

- one or more phosphate groups
- a pentose sugar: either deoxyribose or ribose
- a nitrogen-containing base: adenine, cytosine, guanine, thymine, or uracil

Nucleotides can be assembled into nucleic acids (DNA or RNA) or the energy compound adenosine triphosphate.

Nucleotides



(a) The building blocks of all nucleotides are one or more phosphate groups, a pentose sugar, and a nitrogencontaining base. (b) The nitrogen-containing bases of nucleotides. (c) The two pentose sugars of DNA and RNA.

Nucleic Acids

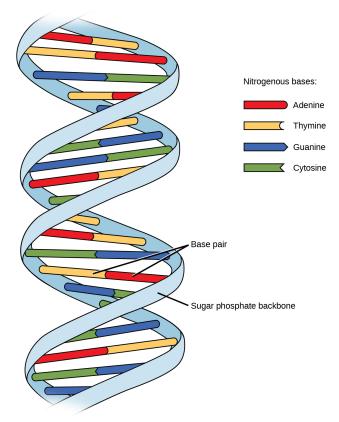
The nucleic acids differ in their type of pentose sugar. **Deoxyribonucleic acid (DNA)** is nucleotide that stores genetic information. DNA contains deoxyribose (so-called because it has one less atom of oxygen than ribose) plus one phosphate group and one nitrogen-containing base. The "choices" of base for DNA are adenine, cytosine, guanine, and thymine. **Ribonucleic acid (RNA)** is a ribose-containing nucleotide that helps manifest the genetic code as protein. RNA contains ribose, one phosphate group, and one nitrogen-containing base, but the "choices" of base for RNA are adenine, cytosine, guanine, and uracil.

The nitrogen-containing bases adenine and guanine are classified as purines. A **purine** is a nitrogen-containing molecule with a double ring structure, which accommodates several nitrogen atoms. The bases cytosine, thymine (found in DNA only) and uracil (found in RNA only) are pyramidines. A **pyramidine** is a nitrogen-containing base with a single ring structure

Bonds formed by dehydration synthesis between the pentose sugar of one nucleic acid monomer and the phosphate group of another form a "backbone," from which the components' nitrogen-containing bases protrude. In DNA, two such backbones attach at their protruding bases via hydrogen bonds. These twist to form a shape known as a double helix ([link]). The sequence of nitrogen-containing bases within a strand of DNA form the genes that act as a molecular code instructing cells in the assembly of amino acids into proteins. Humans have almost 22,000 genes in their DNA, locked up in the 46 chromosomes inside the nucleus of each cell

(except red blood cells which lose their nuclei during development). These genes carry the genetic code to build one's body, and are unique for each individual except identical twins.

DNA



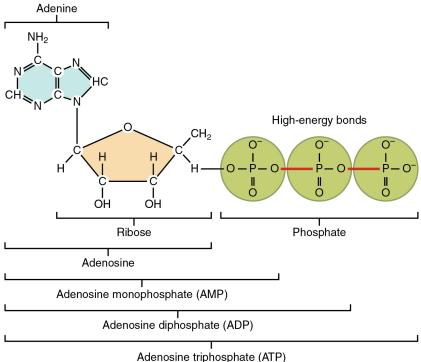
In the DNA double helix, two strands attach via hydrogen bonds between the bases of the component nucleotides.

In contrast, RNA consists of a single strand of sugar-phosphate backbone studded with bases. Messenger RNA (mRNA) is created during protein synthesis to carry the genetic instructions from the DNA to the cell's protein manufacturing plants in the cytoplasm, the ribosomes.

Adenosine Triphosphate

The nucleotide adenosine triphosphate (ATP), is composed of a ribose sugar, an adenine base, and three phosphate groups ([link]). ATP is classified as a high energy compound because the two covalent bonds linking its three phosphates store a significant amount of potential energy. In the body, the energy released from these high energy bonds helps fuel the body's activities, from muscle contraction to the transport of substances in and out of cells to anabolic chemical reactions.

Structure of Adenosine Triphosphate (ATP)



When a phosphate group is cleaved from ATP, the products are adenosine diphosphate (ADP) and inorganic phosphate (P_i). This hydrolysis reaction can be written:

Equation:

$$ATP + H_2O \ \rightarrow \ ADP + P_i + energy$$

Removal of a second phosphate leaves adenosine monophosphate (AMP) and two phosphate groups. Again, these reactions also liberate the energy that had been stored in the phosphate-phosphate bonds. They are reversible,

too, as when ADP undergoes phosphorylation. **Phosphorylation** is the addition of a phosphate group to an organic compound, in this case, resulting in ATP. In such cases, the same level of energy that had been released during hydrolysis must be reinvested to power dehydration synthesis.

Cells can also transfer a phosphate group from ATP to another organic compound. For example, when glucose first enters a cell, a phosphate group is transferred from ATP, forming glucose phosphate ($C_6H_{12}O_6$ —P) and ADP. Once glucose is phosphorylated in this way, it can be stored as glycogen or metabolized for immediate energy.

Chapter Review

Organic compounds essential to human functioning include carbohydrates, lipids, proteins, and nucleotides. These compounds are said to be organic because they contain both carbon and hydrogen. Carbon atoms in organic compounds readily share electrons with hydrogen and other atoms, usually oxygen, and sometimes nitrogen. Carbon atoms also may bond with one or more functional groups such as carboxyls, hydroxyls, aminos, or phosphates. Monomers are single units of organic compounds. They bond by dehydration synthesis to form polymers, which can in turn be broken by hydrolysis.

Carbohydrate compounds provide essential body fuel. Their structural forms include monosaccharides such as glucose, disaccharides such as lactose, and polysaccharides, including starches (polymers of glucose), glycogen (the storage form of glucose), and fiber. All body cells can use glucose for fuel. It is converted via an oxidation-reduction reaction to ATP.

Lipids are hydrophobic compounds that provide body fuel and are important components of many biological compounds. Triglycerides are the most abundant lipid in the body, and are composed of a glycerol backbone attached to three fatty acid chains. Phospholipids are compounds composed of a diglyceride with a phosphate group attached at the molecule's head. The result is a molecule with polar and nonpolar regions. Steroids are lipids

formed of four hydrocarbon rings. The most important is cholesterol. Prostaglandins are signaling molecules derived from unsaturated fatty acids.

Proteins are critical components of all body tissues. They are made up of monomers called amino acids, which contain nitrogen, joined by peptide bonds. Protein shape is critical to its function. Most body proteins are globular. An example is enzymes, which catalyze chemical reactions.

Nucleotides are compounds with three building blocks: one or more phosphate groups, a pentose sugar, and a nitrogen-containing base. DNA and RNA are nucleic acids that function in protein synthesis. ATP is the body's fundamental molecule of energy transfer. Removal or addition of phosphates releases or invests energy.

Glossary

adenosine triphosphate (ATP)

nucleotide containing ribose and an adenine base that is essential in energy transfer

amino acid

building block of proteins; characterized by an amino and carboxyl functional groups and a variable side-chain

anabolism

assembly of more complex molecules from simpler molecules

carbohydrate

class of organic compounds built from sugars, molecules containing carbon, hydrogen, and oxygen in a 1-2-1 ratio

catabolism

breaking down of more complex molecules into simpler molecules

denaturation

change in the structure of a molecule through physical or chemical means

deoxyribonucleic acid (DNA)

deoxyribose-containing nucleotide that stores genetic information

disaccharide

pair of carbohydrate monomers bonded by dehydration synthesis via a glycosidic bond

disulfide bond

covalent bond formed within a polypeptide between sulfide groups of sulfur-containing amino acids, for example, cysteine

functional group

group of atoms linked by strong covalent bonds that tends to behave as a distinct unit in chemical reactions with other atoms

lipid

class of nonpolar organic compounds built from hydrocarbons and distinguished by the fact that they are not soluble in water

macromolecule

large molecule formed by covalent bonding

metabolism

sum of all of the body's chemical reactions

monosaccharide

monomer of carbohydrate; also known as a simple sugar

nucleotide

class of organic compounds composed of one or more phosphate groups, a pentose sugar, and a base

peptide bond

covalent bond formed by dehydration synthesis between two amino acids

phospholipid

a lipid compound in which a phosphate group is combined with a diglyceride

phosphorylation

addition of one or more phosphate groups to an organic compound

polysaccharide

compound consisting of more than two carbohydrate monomers bonded by dehydration synthesis via glycosidic bonds

prostaglandin

lipid compound derived from fatty acid chains and important in regulating several body processes

protein

class of organic compounds that are composed of many amino acids linked together by peptide bonds

purine

nitrogen-containing base with a double ring structure; adenine and guanine

pyrimidine

nitrogen-containing base with a single ring structure; cytosine, thiamine, and uracil

ribonucleic acid (RNA)

ribose-containing nucleotide that helps manifest the genetic code as protein

steroid

(also, sterol) lipid compound composed of four hydrocarbon rings bonded to a variety of other atoms and molecules

substrate

reactant in an enzymatic reaction

triglyceride

lipid compound composed of a glycerol molecule bonded with three fatty acid chains

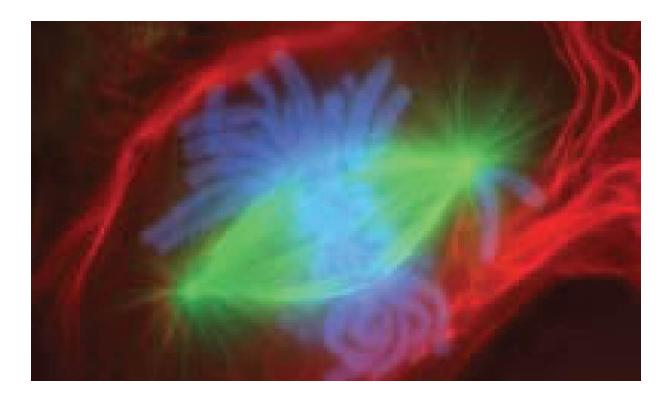
OU Human Physiology: Cellular Introduction class="introduction"

By the end of this section, you will be able to:

- Explain the relationship between structural and functional cell
- Describe the primary responsibility of a cell

Fluorescence-stained Cell Undergoing Mitosis

A lung cell from a newt, commonly studied for its similarity to human lung cells, is stained with fluorescent dyes. The green stain reveals mitotic spindles, red is the cell membrane and part of the cytoplasm, and the structures that appear light blue are chromosomes. This cell is in anaphase of mitosis. (credit: "Mortadelo2005"/Wikimedia Commons)



You developed from a single fertilized egg cell into the complex organism containing trillions of cells that you see when you look in a mirror. During this developmental process, early, undifferentiated cells differentiate and become specialized in their structure and function. These different cell types form specialized tissues that work in concert to perform all of the functions necessary for the living organism. Cellular and developmental biologists study how the continued division of a single cell leads to such complexity and differentiation.

Consider the difference between a structural cell in the skin and a nerve cell. A structural skin cell may be shaped like a flat plate (squamous) and live only for a short time before it is shed and replaced. Packed tightly into rows and sheets, the squamous skin cells provide a protective barrier for the cells and tissues that lie beneath. A nerve cell, on the other hand, may be shaped something like a star, sending out long processes up to a meter in length and may live for the entire lifetime of the organism. With their long winding appendages, nerve cells can communicate with one another and with other types of body cells and send rapid signals that inform the organism about its environment and allow it to interact with that environment. These differences illustrate one very important theme that is

consistent at all organizational levels of biology: the form of a structure is optimally suited to perform particular functions assigned to that structure. Keep this theme in mind as you tour the inside of a cell and are introduced to the various types of cells in the body.

A primary responsibility of each cell is to contribute to homeostasis. Homeostasis is a term used in biology that refers to a dynamic state of balance within parameters that are compatible with life. For example, living cells require a water-based environment to survive in, and there are various physical (anatomical) and physiological mechanisms that keep all of the trillions of living cells in the human body moist. This is one aspect of homeostasis. When a particular parameter, such as blood pressure or blood oxygen content, moves far enough *out* of homeostasis (generally becoming too high or too low), illness or disease—and sometimes death—inevitably results.

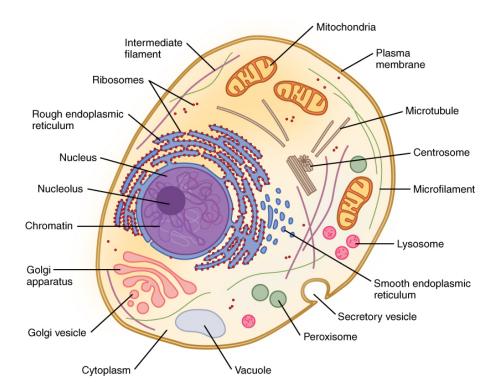
The concept of a cell started with microscopic observations of dead cork tissue by scientist Robert Hooke in 1665. Without realizing their function or importance, Hook coined the term "cell" based on the resemblance of the small subdivisions in the cork to the rooms that monks inhabited, called cells. About ten years later, Antonie van Leeuwenhoek became the first person to observe living and moving cells under a microscope. In the century that followed, the theory that cells represented the basic unit of life would develop. These tiny fluid-filled sacs house components responsible for the thousands of biochemical reactions necessary for an organism to grow and survive. In this chapter, you will learn about the major components and functions of a prototypical, generalized cell and discover some of the different types of cells in the human body.

OU Human Physiology: The Cytoplasm and Cellular Organelles By the end of this section, you will be able to:

- Describe the structure and function of the cellular organelles including the endoplasmic reticulum, golgi apparatus, lysosome, mitochondria, ribosomes, and peroxisomes
- Integrate and synthesize chemistry knowledge of macromolecules such as proteins, lipids, carbohydrates, and nucleotides to functions of cellular organelles

All living cells in multicellular organisms contain an internal cytoplasmic compartment, and a nucleus within the cytoplasm. **Cytosol**, the jelly-like substance within the cell, provides the fluid medium necessary for biochemical reactions. Eukaryotic cells, including all animal cells, also contain various cellular organelles. An **organelle** ("little organ") is one of several different types of membrane-enclosed bodies in the cell, each performing a unique function. Just as the various bodily organs work together in harmony to perform all of a human's functions, the many different cellular organelles work together to keep the cell healthy and performing all of its important functions. The organelles and cytosol, taken together, compose the cell's **cytoplasm**. The **nucleus** is a cell's central organelle, which contains the cell's DNA ([link]).

Prototypical Human Cell



While this image is not indicative of any one particular human cell, it is a prototypical example of a cell containing the primary organelles and internal structures.

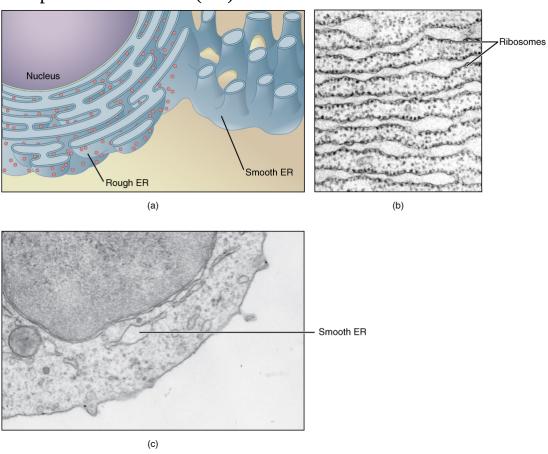
Organelles of the Endomembrane System

A set of three major organelles together form a system within the cell called the endomembrane system. These organelles work together to perform various cellular jobs, including the task of producing, packaging, and exporting certain cellular products. The organelles of the endomembrane system include the endoplasmic reticulum, Golgi apparatus, and vesicles.

Endoplasmic Reticulum

The **endoplasmic reticulum (ER)** is a system of channels that is continuous with the nuclear membrane (or "envelope") covering the nucleus and composed of the same lipid bilayer material. The ER can be thought of as a series of winding thoroughfares similar to the waterway canals in Venice. The ER provides passages throughout much of the cell that function in transporting, synthesizing, and storing materials. The winding structure of the ER results in a large membranous surface area that supports its many functions ([link]).

Endoplasmic Reticulum (ER)



(a) The ER is a winding network of thin membranous sacs found in close association with the cell nucleus. The smooth and rough endoplasmic reticula are very different in appearance and function (source: mouse tissue). (b) Rough ER is studded with numerous ribosomes, which are sites of protein synthesis (source: mouse tissue). EM × 110,000. (c) Smooth ER synthesizes phospholipids, steroid hormones, regulates the concentration of cellular Ca⁺⁺, metabolizes some

carbohydrates, and breaks down certain toxins (source: mouse tissue). EM × 110,510. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

Endoplasmic reticulum can exist in two forms: rough ER and smooth ER. These two types of ER perform some very different functions and can be found in very different amounts depending on the type of cell. Rough ER (RER) is so-called because its membrane is dotted with embedded granules —organelles called ribosomes, giving the RER a bumpy appearance. A **ribosome** is an organelle that serves as the site of protein synthesis. It is composed of two ribosomal RNA subunits that wrap around mRNA to start the process of translation, followed by protein synthesis. Smooth ER (SER) lacks these ribosomes.

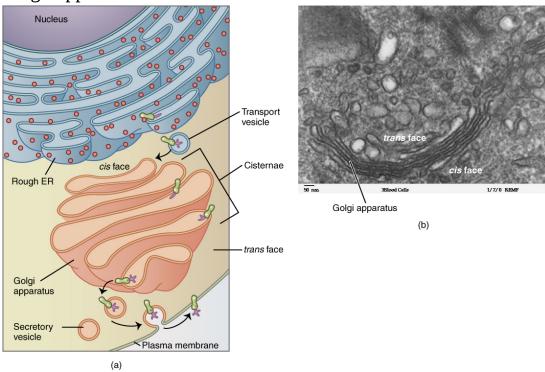
One of the main functions of the smooth ER is in the synthesis of lipids. The smooth ER synthesizes phospholipids, the main component of biological membranes, as well as steroid hormones. For this reason, cells that produce large quantities of such hormones, such as those of the female ovaries and male testes, contain large amounts of smooth ER. In addition to lipid synthesis, the smooth ER also sequesters (i.e., stores) and regulates the concentration of cellular Ca⁺⁺, a function extremely important in cells of the nervous system where Ca⁺⁺ is the trigger for neurotransmitter release. The smooth ER additionally metabolizes some carbohydrates and performs a detoxification role, breaking down certain toxins.

In contrast with the smooth ER, the primary job of the rough ER is the synthesis and modification of proteins destined for the cell membrane or for export from the cell. For this protein synthesis, many ribosomes attach to the ER (giving it the studded appearance of rough ER). Typically, a protein is synthesized within the ribosome and released inside the channel of the rough ER, where sugars can be added to it (by a process called glycosylation) before it is transported within a vesicle to the next stage in the packaging and shipping process: the Golgi apparatus.

The Golgi Apparatus

The **Golgi apparatus** is responsible for sorting, modifying, and shipping off the products that come from the rough ER, much like a post-office. The Golgi apparatus looks like stacked flattened discs, almost like stacks of oddly shaped pancakes. Like the ER, these discs are membranous. The Golgi apparatus has two distinct sides, each with a different role. One side (called the cis face) of the apparatus receives products in vesicles. These products are sorted through the apparatus, and then they are released from the opposite side (called the trans face) after being repackaged into new vesicles. If the product is to be exported from the cell, the vesicle migrates to the cell surface and fuses to the cell membrane, and the cargo is secreted ([link]).

Golgi Apparatus



(a) The Golgi apparatus manipulates products from the rough ER, and also produces new organelles called lysosomes. Proteins and other products of the ER are sent to the Golgi apparatus, which organizes, modifies, packages, and tags them. Some of these products are transported to other areas of the cell and some are exported from the cell through exocytosis.

Enzymatic proteins are packaged as new lysosomes (or packaged and sent for fusion with existing lysosomes). (b) An electron micrograph of the Golgi apparatus.

Lysosomes

Some of the protein products packaged by the Golgi include digestive enzymes that are meant to remain inside the cell for use in breaking down certain materials. The enzyme-containing vesicles released by the Golgi may form new lysosomes, or fuse with existing, lysosomes. A **lysosome** is an organelle that contains enzymes that break down and digest unneeded cellular components, such as a damaged organelle. (A lysosome is similar to a wrecking crew that takes down old and unsound buildings in a neighborhood.) **Autophagy** ("self-eating") is the process of a cell digesting its own structures. Lysosomes are also important for breaking down foreign material. For example, when certain immune defense cells (white blood cells) phagocytize bacteria, the bacterial cell is transported into a lysosome and digested by the enzymes inside. As one might imagine, such phagocytic defense cells contain large numbers of lysosomes.

Under certain circumstances, lysosomes perform a more grand and dire function. In the case of damaged or unhealthy cells, lysosomes can be triggered to open up and release their digestive enzymes into the cytoplasm of the cell, killing the cell. This "self-destruct" mechanism is called **autolysis**, and makes the process of cell death controlled (a mechanism called "apoptosis").

No	ote:			



Watch this <u>video</u> to learn about the endomembrane system, which includes the rough and smooth ER and the Golgi body as well as lysosomes and vesicles. What is the primary role of the endomembrane system?

Organelles for Energy Production and Detoxification

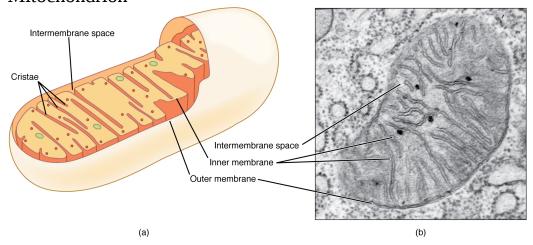
In addition to the jobs performed by the endomembrane system, the cell has many other important functions. Just as you must consume nutrients to provide yourself with energy, so must each of your cells take in nutrients, some of which convert to chemical energy that can be used to power biochemical reactions. Another important function of the cell is detoxification. Humans take in all sorts of toxins from the environment and also produce harmful chemicals as byproducts of cellular processes. Cells called hepatocytes in the liver detoxify many of these toxins.

Mitochondria

A **mitochondrion** (plural = mitochondria) is a membranous, bean-shaped organelle that is the "power-house" of the cell. Mitochondria consist of an outer lipid bilayer membrane as well as an additional inner lipid bilayer membrane called the cristae ([link]). The space inside the cristae is called the matrix and the area between the cristae and the outer membrane is called the intermembrane space. These structures are very important as they provide a location for many biochemical reactions of cellular respiration. These reactions convert energy stored in nutrient molecules (such as glucose) into adenosine triphosphate (ATP), which provides usable cellular energy to the cell. Cells use ATP constantly, and so the mitochondria are constantly at work. Oxygen molecules are required during cellular

respiration, which is why you must constantly breathe it in. One of the organ systems in the body that uses huge amounts of ATP is the muscular system because ATP is required to sustain muscle contraction. As a result, muscle cells are packed full of mitochondria. Nerve cells also need large quantities of ATP to run their sodium-potassium pumps. Therefore, an individual neuron will be loaded with over a thousand mitochondria. On the other hand, a bone cell, which is not nearly as metabolically-active, might only have a couple hundred mitochondria.

Mitochondrion



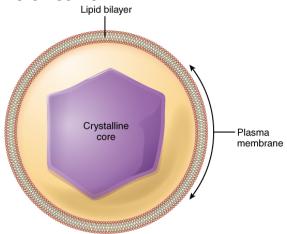
The mitochondria are the energy-conversion factories of the cell. (a) A mitochondrion is composed of two separate lipid bilayer membranes. Along the inner membrane are various molecules that work together to produce ATP, the cell's major energy currency. (b) An electron micrograph of mitochondria. EM × 236,000. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Peroxisomes

Like lysosomes, a **peroxisome** is a membrane-bound cellular organelle that contains mostly enzymes ([link]). Peroxisomes perform a couple of

different functions, including lipid metabolism and chemical detoxification. In contrast to the digestive enzymes found in lysosomes, the enzymes within peroxisomes serve to transfer hydrogen atoms from various molecules to oxygen, producing hydrogen peroxide (H_2O_2) . In this way, peroxisomes neutralize poisons such as alcohol. In order to appreciate the importance of peroxisomes, it is necessary to understand the concept of reactive oxygen species.

Peroxisome



Peroxisomes are membranebound organelles that contain an abundance of enzymes for detoxifying harmful substances and lipid metabolism.

Reactive oxygen species (ROS) such as peroxides and free radicals are the highly reactive products of many normal cellular processes, including the mitochondrial reactions that produce ATP and oxygen metabolism. Examples of ROS include the hydroxyl radical OH, H_2O_2 , and superoxide (O_2^-). Some ROS are important for certain cellular functions, such as cell signaling processes and immune responses against foreign substances. Free radicals are reactive because they contain free unpaired electrons; they can easily oxidize other molecules throughout the cell, causing cellular damage

and even cell death. Free radicals are thought to play a role in many destructive processes in the body, from cancer to coronary artery disease.

Peroxisomes, on the other hand, oversee reactions that neutralize free radicals. Peroxisomes produce large amounts of the toxic H_2O_2 in the process, but peroxisomes contain enzymes that convert H_2O_2 into water and oxygen. These byproducts are safely released into the cytoplasm. Like miniature sewage treatment plants, peroxisomes neutralize harmful toxins so that they do not wreak havoc in the cells. The liver is the organ primarily responsible for detoxifying the blood before it travels throughout the body, and liver cells contain an exceptionally high number of peroxisomes.

Defense mechanisms such as detoxification within the peroxisome and certain cellular antioxidants serve to neutralize many of these molecules. Some vitamins and other substances, found primarily in fruits and vegetables, have antioxidant properties. Antioxidants work by being oxidized themselves, halting the destructive reaction cascades initiated by the free radicals. Sometimes though, ROS accumulate beyond the capacity of such defenses.

Oxidative stress is the term used to describe damage to cellular components caused by ROS. Due to their characteristic unpaired electrons, ROS can set off chain reactions where they remove electrons from other molecules, which then become oxidized and reactive, and do the same to other molecules, causing a chain reaction. ROS can cause permanent damage to cellular lipids, proteins, carbohydrates, and nucleic acids. Damaged DNA can lead to genetic mutations and even cancer. A **mutation** is a change in the nucleotide sequence in a gene within a cell's DNA, potentially altering the protein coded by that gene. Other diseases believed to be triggered or exacerbated by ROS include Alzheimer's disease, cardiovascular diseases, diabetes, Parkinson's disease, arthritis, Huntington's disease, and schizophrenia, among many others. It is noteworthy that these diseases are largely age-related. Many scientists believe that oxidative stress is a major contributor to the aging process.

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Aging and the...

Cell: The Free Radical Theory

The free radical theory on aging was originally proposed in the 1950s, and still remains under debate. Generally speaking, the free radical theory of aging suggests that accumulated cellular damage from oxidative stress contributes to the physiological and anatomical effects of aging. There are two significantly different versions of this theory: one states that the aging process itself is a result of oxidative damage, and the other states that oxidative damage causes age-related disease and disorders. The latter version of the theory is more widely accepted than the former. However, many lines of evidence suggest that oxidative damage does contribute to the aging process. Research has shown that reducing oxidative damage can result in a longer lifespan in certain organisms such as yeast, worms, and fruit flies. Conversely, increasing oxidative damage can shorten the lifespan of mice and worms. Interestingly, a manipulation called calorierestriction (moderately restricting the caloric intake) has been shown to increase life span in some laboratory animals. It is believed that this increase is at least in part due to a reduction of oxidative stress. However, a long-term study of primates with calorie-restriction showed no increase in their lifespan. A great deal of additional research will be required to better understand the link between reactive oxygen species and aging.

The Cytoskeleton

Much like the bony skeleton structurally supports the human body, the cytoskeleton helps the cells to maintain their structural integrity. The **cytoskeleton** is a group of fibrous proteins that provide structural support for cells, but this is only one of the functions of the cytoskeleton. Cytoskeletal components are also critical for cell motility, cell reproduction, and transportation of substances within the cell.

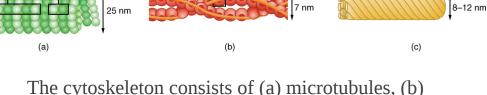
The cytoskeleton forms a complex thread-like network throughout the cell consisting of three different kinds of protein-based filaments: microfilaments, intermediate filaments, and microtubules ([link]). The thickest of the three is the **microtubule**, a structural filament composed of

subunits of a protein called tubulin. Microtubules maintain cell shape and structure, help resist compression of the cell, and play a role in positioning the organelles within the cell. Microtubules also make up two types of cellular appendages important for motion: cilia and flagella. **Cilia** are found on many cells of the body, including the epithelial cells that line the airways of the respiratory system. Cilia move rhythmically; they beat constantly, moving waste materials such as dust, mucus, and bacteria upward through the airways, away from the lungs and toward the mouth. Beating cilia on cells in the female fallopian tubes move egg cells from the ovary towards the uterus. A **flagellum** (plural = flagella) is an appendage larger than a cilium and specialized for cell locomotion. The only flagellated cell in humans is the sperm cell that must propel itself towards female egg cells.

The Three Components of the Cytoskeleton

Column of

Tubulin



Actin subunit

Fibrous subunit

(keratins coiled together)

The cytoskeleton consists of (a) microfubules, (b) microfilaments, and (c) intermediate filaments. The cytoskeleton plays an important role in maintaining cell shape and structure, promoting cellular movement, and aiding cell division.

A very important function of microtubules is to set the paths (somewhat like railroad tracks) along which the genetic material can be pulled (a process requiring ATP) during cell division, so that each new daughter cell receives the appropriate set of chromosomes. Two short, identical

microtubule structures called centrioles are found near the nucleus of cells. A **centriole** can serve as the cellular origin point for microtubules extending outward as cilia or flagella or can assist with the separation of DNA during cell division. Microtubules grow out from the centrioles by adding more tubulin subunits, like adding additional links to a chain.

In contrast with microtubules, the **microfilament** is a thinner type of cytoskeletal filament (see [link]b). Actin, a protein that forms chains, is the primary component of these microfilaments. Actin fibers, twisted chains of actin filaments, constitute a large component of muscle tissue and, along with the protein myosin, are responsible for muscle contraction. Like microtubules, actin filaments are long chains of single subunits (called actin subunits). In muscle cells, these long actin strands, called thin filaments, are "pulled" by thick filaments of the myosin protein to contract the cell.

Actin also has an important role during cell division. When a cell is about to split in half during cell division, actin filaments work with myosin to create a cleavage furrow that eventually splits the cell down the middle, forming two new cells from the original cell.

The final cytoskeletal filament is the intermediate filament. As its name would suggest, an **intermediate filament** is a filament intermediate in thickness between the microtubules and microfilaments (see [link]c). Intermediate filaments are made up of long fibrous subunits of a protein called keratin that are wound together like the threads that compose a rope. Intermediate filaments, in concert with the microtubules, are important for maintaining cell shape and structure. Unlike the microtubules, which resist compression, intermediate filaments resist tension—the forces that pull apart cells. There are many cases in which cells are prone to tension, such as when epithelial cells of the skin are compressed, tugging them in different directions. Intermediate filaments help anchor organelles together within a cell and also link cells to other cells by forming special cell-to-cell junctions.

Chapter Review

The internal environmental of a living cell is made up of a fluid, jelly-like substance called cytosol, which consists mainly of water, but also contains various dissolved nutrients and other molecules. The cell contains an array of cellular organelles, each one performing a unique function and helping to maintain the health and activity of the cell. The cytosol and organelles together compose the cell's cytoplasm. Most organelles are surrounded by a lipid membrane similar to the cell membrane of the cell. The endoplasmic reticulum (ER), Golgi apparatus, and lysosomes share a functional connectivity and are collectively referred to as the endomembrane system. There are two types of ER: smooth and rough. While the smooth ER performs many functions, including lipid synthesis and ion storage, the rough ER is mainly responsible for protein synthesis using its associated ribosomes. The rough ER sends newly made proteins to the Golgi apparatus where they are modified and packaged for delivery to various locations within or outside of the cell. Some of these protein products are enzymes destined to break down unwanted material and are packaged as lysosomes for use inside the cell.

Cells also contain mitochondria and peroxisomes, which are the organelles responsible for producing the cell's energy supply and detoxifying certain chemicals, respectively. Biochemical reactions within mitochondria transform energy-carrying molecules into the usable form of cellular energy known as ATP. Peroxisomes contain enzymes that transform harmful substances such as free radicals into oxygen and water. Cells also contain a miniaturized "skeleton" of protein filaments that extend throughout its interior. Three different kinds of filaments compose this cytoskeleton (in order of increasing thickness): microfilaments, intermediate filaments, and microtubules. Each cytoskeletal component performs unique functions as well as provides a supportive framework for the cell.

Glossary

autolysis

breakdown of cells by their own enzymatic action

autophagy

lysosomal breakdown of a cell's own components

centriole

small, self-replicating organelle that provides the origin for microtubule growth and moves DNA during cell division

cilia

small appendage on certain cells formed by microtubules and modified for movement of materials across the cellular surface

cytoplasm

internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials

cytoskeleton

"skeleton" of a cell; formed by rod-like proteins that support the cell's shape and provide, among other functions, locomotive abilities

cytosol

clear, semi-fluid medium of the cytoplasm, made up mostly of water

endoplasmic reticulum (ER)

cellular organelle that consists of interconnected membrane-bound tubules, which may or may not be associated with ribosomes (rough type or smooth type, respectively)

flagellum

appendage on certain cells formed by microtubules and modified for movement

Golgi apparatus

cellular organelle formed by a series of flattened, membrane-bound sacs that functions in protein modification, tagging, packaging, and transport

intermediate filament

type of cytoskeletal filament made of keratin, characterized by an intermediate thickness, and playing a role in resisting cellular tension

lysosome

membrane-bound cellular organelle originating from the Golgi apparatus and containing digestive enzymes

microfilament

the thinnest of the cytoskeletal filaments; composed of actin subunits that function in muscle contraction and cellular structural support

microtubule

the thickest of the cytoskeletal filaments, composed of tubulin subunits that function in cellular movement and structural support

mitochondrion

one of the cellular organelles bound by a double lipid bilayer that function primarily in the production of cellular energy (ATP)

mutation

change in the nucleotide sequence in a gene within a cell's DNA

nucleus

cell's central organelle; contains the cell's DNA

organelle

any of several different types of membrane-enclosed specialized structures in the cell that perform specific functions for the cell

peroxisome

membrane-bound organelle that contains enzymes primarily responsible for detoxifying harmful substances

reactive oxygen species (ROS)

a group of extremely reactive peroxides and oxygen-containing radicals that may contribute to cellular damage

ribosome

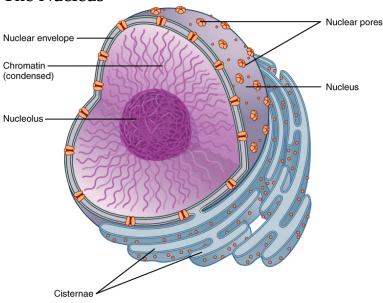
cellular organelle that functions in protein synthesis

OU Human Physiology: The Nucleus and DNA Replication By the end of this section, you will be able to:

- Describe the structure and features of the nuclear membrane
- List the contents of the nucleus
- Explain the organization of the DNA molecule within the nucleus
- Describe the process of DNA replication

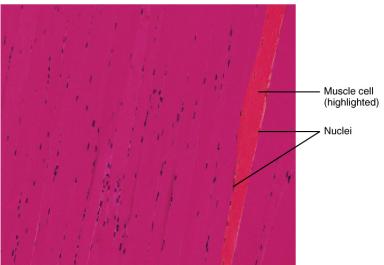
The nucleus is the largest and most prominent of a cell's organelles ([link]). The nucleus is generally considered the control center of the cell because it stores all of the genetic instructions for manufacturing proteins. Interestingly, some cells in the body, such as muscle cells, contain more than one nucleus ([link]), which is known as multinucleated. Other cells, such as mammalian red blood cells (RBCs), do not contain nuclei at all. RBCs eject their nuclei as they mature, making space for the large numbers of hemoglobin molecules that carry oxygen throughout the body ([link]). Without nuclei, the life span of RBCs is short, and so the body must produce new ones constantly.

The Nucleus



The nucleus is the control center of the cell. The nucleus of living cells contains the genetic material that determines the entire structure and function of that cell.

Multinucleate Muscle Cell



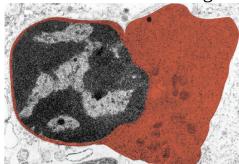
Unlike cardiac muscle cells and smooth muscle cells, which have a single nucleus, a skeletal muscle cell contains many nuclei, and is referred to as "multinucleated." These muscle cells are long and fibrous (often referred to as muscle fibers). During development, many smaller cells fuse to form a mature muscle fiber. The nuclei of the fused cells are conserved in the mature cell, thus imparting a multinucleate characteristic to mature muscle cells. LM × 104.3. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

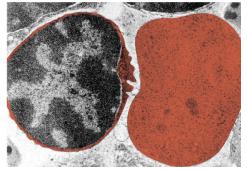
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View the University of Michigan WebScope at http://141.214.65.171/Histology/Basic%20Tissues/Muscle/058thin HISTO83X.svs/view.apml to explore the tissue sample in greater detail.

Red Blood Cell Extruding Its Nucleus





Mature red blood cells lack a nucleus. As they mature, erythroblasts extrude their nucleus, making room for more hemoglobin. The two panels here show an erythroblast before and after ejecting its nucleus, respectively. (credit: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)

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Inside the nucleus lies the blueprint that dictates everything a cell will do and all of the products it will make. This information is stored within DNA. The nucleus sends "commands" to the cell via molecular messengers that translate the information from DNA. Each cell in your body (with the exception of germ cells) contains the complete set of your DNA. When a cell divides, the DNA must be duplicated so that the each new cell receives a full complement of DNA. The following section will explore the structure of the nucleus and its contents, as well as the process of DNA replication.

Organization of the Nucleus and Its DNA

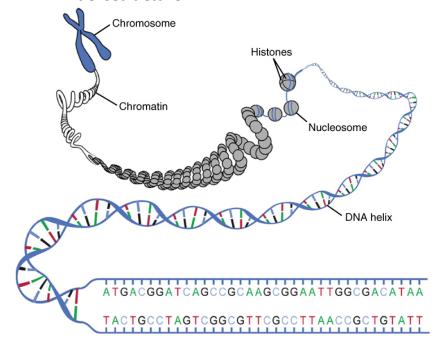
Like most other cellular organelles, the nucleus is surrounded by a membrane called the **nuclear envelope**. This membranous covering consists of two adjacent lipid bilayers with a thin fluid space in between them. Spanning these two bilayers are nuclear pores. A **nuclear pore** is a tiny passageway for the passage of proteins, RNA, and solutes between the nucleus and the cytoplasm. Proteins called pore complexes lining the nuclear pores regulate the passage of materials into and out of the nucleus.

Inside the nuclear envelope is a gel-like nucleoplasm with solutes that include the building blocks of nucleic acids. There also can be a dark-staining mass often visible under a simple light microscope, called a **nucleolus** (plural = nucleoli). The nucleolus is a region of the nucleus that is responsible for manufacturing the RNA necessary for construction of

ribosomes. Once synthesized, newly made ribosomal subunits exit the cell's nucleus through the nuclear pores.

The genetic instructions that are used to build and maintain an organism are arranged in an orderly manner in strands of DNA. Within the nucleus are threads of **chromatin** composed of DNA and associated proteins ([link]). Along the chromatin threads, the DNA is wrapped around a set of **histone** proteins. A **nucleosome** is a single, wrapped DNA-histone complex. Multiple nucleosomes along the entire molecule of DNA appear like a beaded necklace, in which the string is the DNA and the beads are the associated histones. When a cell is in the process of division, the chromatin condenses into chromosomes, so that the DNA can be safely transported to the "daughter cells." The **chromosome** is composed of DNA and proteins; it is the condensed form of chromatin. It is estimated that humans have almost 22,000 genes distributed on 46 chromosomes.

DNA Macrostructure



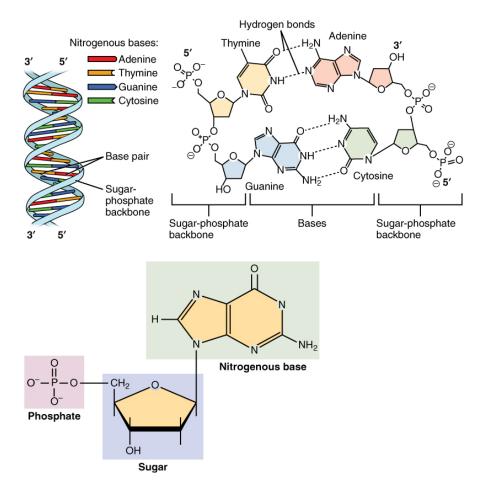
Strands of DNA are wrapped around supporting histones. These proteins are increasingly bundled and condensed into chromatin, which is packed tightly into chromosomes when the cell is ready to divide.

DNA Replication

In order for an organism to grow, develop, and maintain its health, cells must reproduce themselves by dividing to produce two new daughter cells, each with the full complement of DNA as found in the original cell. Billions of new cells are produced in an adult human every day. Only very few cell types in the body do not divide, including nerve cells, skeletal muscle fibers, and cardiac muscle cells. The division time of different cell types varies. Epithelial cells of the skin and gastrointestinal lining, for instance, divide very frequently to replace those that are constantly being rubbed off of the surface by friction.

A DNA molecule is made of two strands that "complement" each other in the sense that the molecules that compose the strands fit together and bind to each other, creating a double-stranded molecule that looks much like a long, twisted ladder. Each side rail of the DNA ladder is composed of alternating sugar and phosphate groups ([link]). The two sides of the ladder are not identical, but are complementary. These two backbones are bonded to each other across pairs of protruding bases, each bonded pair forming one "rung," or cross member. The four DNA bases are adenine (A), thymine (T), cytosine (C), and guanine (G). Because of their shape and charge, the two bases that compose a pair always bond together. Adenine always binds with thymine, and cytosine always binds with guanine. The particular sequence of bases along the DNA molecule determines the genetic code. Therefore, if the two complementary strands of DNA were pulled apart, you could infer the order of the bases in one strand from the bases in the other, complementary strand. For example, if one strand has a region with the sequence AGTGCCT, then the sequence of the complementary strand would be TCACGGA.

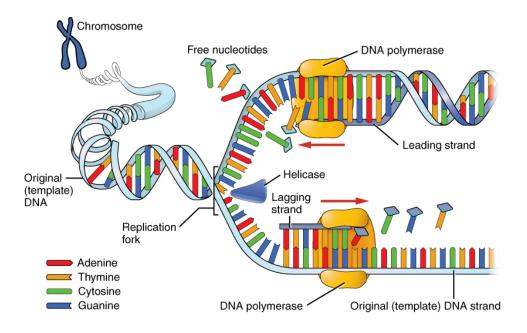
Molecular Structure of DNA



The DNA double helix is composed of two complementary strands. The strands are bonded together via their nitrogenous base pairs using hydrogen bonds.

DNA replication is the copying of DNA that occurs before cell division can take place. After a great deal of debate and experimentation, the general method of DNA replication was deduced in 1958 by two scientists in California, Matthew Meselson and Franklin Stahl. This method is illustrated in [link] and described below.

DNA Replication



DNA replication faithfully duplicates the entire genome of the cell. During DNA replication, a number of different enzymes work together to pull apart the two strands so each strand can be used as a template to synthesize new complementary strands. The two new daughter DNA molecules each contain one preexisting strand and one newly synthesized strand.

Thus, DNA replication is said to be "semiconservative."

Stage 1: Initiation. The two complementary strands are separated, much like unzipping a zipper. Special enzymes, including helicase, untwist and separate the two strands of DNA.

Stage 2: Elongation. Each strand becomes a template along which a new complementary strand is built. DNA polymerase brings in the correct bases to complement the template strand, synthesizing a new strand base by base. A DNA polymerase is an enzyme that adds free nucleotides to the end of a chain of DNA, making a new double strand. This growing strand continues to be built until it has fully complemented the template strand.

Stage 3: Termination. Once the two original strands are bound to their own, finished, complementary strands, DNA replication is stopped and the two new identical DNA molecules are complete.

Each new DNA molecule contains one strand from the original molecule and one newly synthesized strand. The term for this mode of replication is "semiconservative," because half of the original DNA molecule is conserved in each new DNA molecule. This process continues until the cell's entire genome, the entire complement of an organism's DNA, is replicated. As you might imagine, it is very important that DNA replication take place precisely so that new cells in the body contain the exact same genetic material as their parent cells. Mistakes made during DNA replication, such as the accidental addition of an inappropriate nucleotide, have the potential to render a gene dysfunctional or useless. Fortunately, there are mechanisms in place to minimize such mistakes. A DNA proofreading process enlists the help of special enzymes that scan the newly synthesized molecule for mistakes and corrects them. Once the process of DNA replication is complete, the cell is ready to divide. You will explore the process of cell division later in the chapter.

Note:



Watch this <u>video</u> to learn about DNA replication. DNA replication proceeds simultaneously at several sites on the same molecule. What separates the base pair at the start of DNA replication?

Chapter Review

The nucleus is the command center of the cell, containing the genetic instructions for all of the materials a cell will make (and thus all of its functions it can perform). The nucleus is encased within a membrane of two interconnected lipid bilayers, side-by-side. This nuclear envelope is studded with protein-lined pores that allow materials to be trafficked into and out of the nucleus. The nucleus contains one or more nucleoli, which serve as sites for ribosome synthesis. The nucleus houses the genetic material of the cell: DNA. DNA is normally found as a loosely contained structure called chromatin within the nucleus, where it is wound up and associated with a variety of histone proteins. When a cell is about to divide, the chromatin coils tightly and condenses to form chromosomes.

There is a pool of cells constantly dividing within your body. The result is billions of new cells being created each day. Before any cell is ready to divide, it must replicate its DNA so that each new daughter cell will receive an exact copy of the organism's genome. A variety of enzymes are enlisted during DNA replication. These enzymes unwind the DNA molecule, separate the two strands, and assist with the building of complementary strands along each parent strand. The original DNA strands serve as templates from which the nucleotide sequence of the new strands are determined and synthesized. When replication is completed, two identical DNA molecules exist. Each one contains one original strand and one newly synthesized complementary strand.

Glossary

chromatin

substance consisting of DNA and associated proteins

chromosome

condensed version of chromatin

DNA replication

process of duplicating a molecule of DNA

histone

family of proteins that associate with DNA in the nucleus to form chromatin

nuclear envelope

membrane that surrounds the nucleus; consisting of a double lipid-bilayer

nuclear pore

one of the small, protein-lined openings found scattered throughout the nuclear envelope

nucleolus

small region of the nucleus that functions in ribosome synthesis

nucleosome

unit of chromatin consisting of a DNA strand wrapped around histone proteins

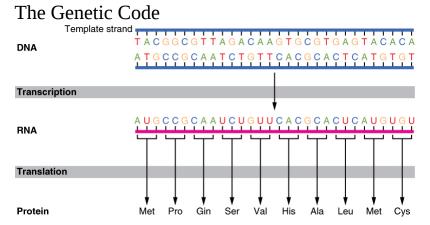
OU Human Physiology: Protein Synthesis By the end of this section, you will be able to:

• List the two major processes of protein synthesis and state the purpose for both of these processes

It was mentioned earlier that DNA provides a "blueprint" for the cell structure and physiology. This refers to the fact that DNA contains the information necessary for the cell to build one very important type of molecule: the protein. Most structural components of the cell are made up, at least in part, by proteins and virtually all the functions that a cell carries out are completed with the help of proteins. One of the most important classes of proteins is enzymes, which help speed up necessary biochemical reactions that take place inside the cell. Some of these critical biochemical reactions include building larger molecules from smaller components (such as occurs during DNA replication or synthesis of microtubules) and breaking down larger molecules into smaller components (such as when harvesting chemical energy from nutrient molecules). Whatever the cellular process may be, it is almost sure to involve proteins. Just as the cell's genome describes its full complement of DNA, a cell's **proteome** is its full complement of proteins. Protein synthesis begins with genes. A gene is a functional segment of DNA that provides the genetic information necessary to build a protein. Each particular gene provides the code necessary to construct a particular protein. **Gene expression**, which transforms the information coded in a gene to a final gene product, ultimately dictates the structure and function of a cell by determining which proteins are made.

The interpretation of genes works in the following way. Recall that proteins are polymers, or chains, of many amino acid building blocks. The sequence of bases in a gene (that is, its sequence of A, T, C, G nucleotides) translates to an amino acid sequence. A triplet is a section of three DNA bases in a row that codes for a specific amino acid. Similar to the way in which the three-letter code *d-o-g* signals the image of a dog, the three-letter DNA base code signals the use of a particular amino acid. For example, the DNA triplet CAC (cytosine, adenine, and cytosine) specifies the amino acid valine. Therefore, a gene, which is composed of multiple triplets in a unique sequence, provides the code to build an entire protein, with multiple amino

acids in the proper sequence ([link]). The mechanism by which cells turn the DNA code into a protein product is a two-step process, with an RNA molecule as the intermediate.



DNA holds all of the genetic information necessary to build a cell's proteins. The nucleotide sequence of a gene is ultimately translated into an amino acid sequence of the gene's corresponding protein.

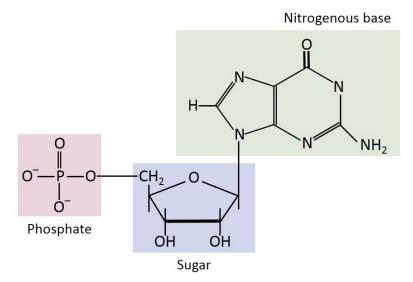
From DNA to RNA: Transcription

DNA is housed within the nucleus, and protein synthesis takes place in the cytoplasm, thus there must be some sort of intermediate messenger that leaves the nucleus and manages protein synthesis. This intermediate messenger is **messenger RNA (mRNA)**, a single-stranded nucleic acid that carries a copy of the genetic code for a single gene out of the nucleus and into the cytoplasm where it is used to produce proteins.

There are several different types of RNA, each having different functions in the cell. The structure of RNA is similar to DNA with a few small exceptions. For one thing, unlike DNA, most types of RNA, including mRNA, are single-stranded and contain no complementary strand. Second, the ribose sugar in RNA contains an additional oxygen atom compared with DNA. Finally, instead of the base thymine, RNA contains the base uracil.

This means that adenine will always pair up with uracil during the protein synthesis process.

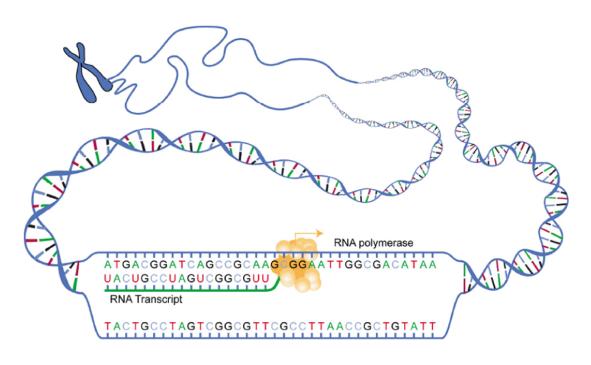
RNA Structure



RNA is comprised of a nitrogenous base, a ribose sugar, and a phosphate group. The structure of RNA is similar to DNA except for an additional oxygen atom on the ribose sugar.

Gene expression begins with the process called **transcription**, which is the synthesis of a strand of mRNA that is complementary to the gene of interest. This process is called transcription because the mRNA is like a transcript, or copy, of the gene's DNA code. Transcription begins in a fashion somewhat like DNA replication, in that a region of DNA unwinds and the two strands separate, however, only that small portion of the DNA will be split apart. The triplets within the gene on this section of the DNA molecule are used as the template to transcribe the complementary strand of RNA ([link]). A codon is a three-base sequence of mRNA, so-called because they directly encode amino acids. Like DNA replication, there are three stages to transcription: initiation, elongation, and termination.

Transcription: from DNA to mRNA



In the first of the two stages of making protein from DNA, a gene on the DNA molecule is transcribed into a complementary mRNA molecule.

Stage 1: *Initiation*. A region at the beginning of the gene called a promoter —a particular sequence of nucleotides—triggers the start of transcription.

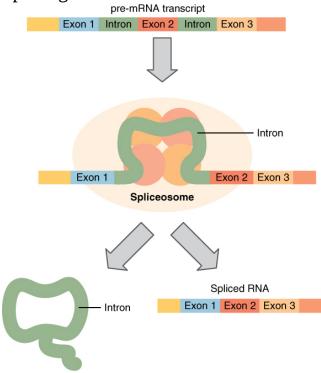
Stage 2: Elongation. Transcription starts when RNA polymerase unwinds the DNA segment. One strand, referred to as the coding strand, becomes the template with the genes to be coded. The polymerase then aligns the correct nucleic acid (A, C, G, or U) with its complementary base on the coding strand of DNA. RNA polymerase is an enzyme that adds new nucleotides to a growing strand of RNA. This process builds a strand of mRNA.

Stage 3: Termination. When the polymerase has reached the end of the gene, one of three specific triplets (UAA, UAG, or UGA) codes a "stop" signal, which triggers the enzymes to terminate transcription and release the mRNA transcript.

Before the mRNA molecule leaves the nucleus and proceeds to protein synthesis, it is modified in a number of ways. For this reason, it is often

called a pre-mRNA at this stage. For example, your DNA, and thus complementary mRNA, contains long regions called non-coding regions that do not code for amino acids. Their function is still a mystery, but the process called splicing removes these non-coding regions from the pre-mRNA transcript ([link]). A spliceosome—a structure composed of various proteins and other molecules—attaches to the mRNA and "splices" or cuts out the non-coding regions. The removed segment of the transcript is called an intron. The remaining exons are pasted together. An exon is a segment of RNA that remains after splicing. Interestingly, some introns that are removed from mRNA are not always non-coding. When different coding regions of mRNA are spliced out, different variations of the protein will eventually result, with differences in structure and function. This process results in a much larger variety of possible proteins and protein functions. When the mRNA transcript is ready, it travels out of the nucleus and into the cytoplasm.

Splicing DNA



In the nucleus, a structure called a spliceosome cuts out introns (noncoding regions) within a pre-

mRNA transcript and reconnects the exons.

From RNA to Protein: Translation

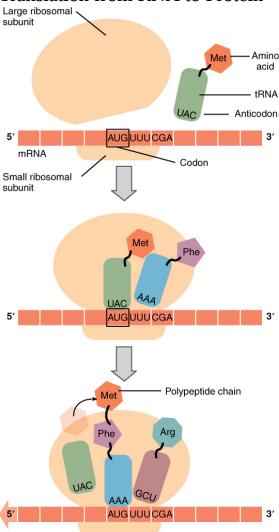
Like translating a book from one language into another, the codons on a strand of mRNA must be translated into the amino acid alphabet of proteins. **Translation** is the process of synthesizing a chain of amino acids called a **polypeptide**. Translation requires two major aids: first, a "translator," the molecule that will conduct the translation, and second, a substrate on which the mRNA strand is translated into a new protein, like the translator's "desk." Both of these requirements are fulfilled by other types of RNA. The substrate on which translation takes place is the ribosome.

Remember that many of a cell's ribosomes are found associated with the rough ER, and carry out the synthesis of proteins destined for the Golgi apparatus. Ribosomal RNA (rRNA) is a type of RNA that, together with proteins, composes the structure of the ribosome. Ribosomes exist in the cytoplasm as two distinct components, a small and a large subunit. When an mRNA molecule is ready to be translated, the two subunits come together and attach to the mRNA. The ribosome provides a substrate for translation, bringing together and aligning the mRNA molecule with the molecular "translators" that must decipher its code.

The other major requirement for protein synthesis is the translator molecules that physically "read" the mRNA codons. Transfer RNA (tRNA) is a type of RNA that ferries the appropriate corresponding amino acids to the ribosome, and attaches each new amino acid to the last, building the polypeptide chain one-by-one. Thus tRNA transfers specific amino acids from the cytoplasm to a growing polypeptide. The tRNA molecules must be able to recognize the codons on mRNA and match them with the correct amino acid. The tRNA is modified for this function. On one end of its structure is a binding site for a specific amino acid. On the other end is a base sequence that matches the codon specifying its particular amino acid. This sequence of three bases on the tRNA molecule is called an anticodon.

For example, a tRNA responsible for shuttling the amino acid glycine contains a binding site for glycine on one end. On the other end it contains an anticodon that complements the glycine codon (GGA is a codon for glycine, and so the tRNAs anticodon would read CCU). Equipped with its particular cargo and matching anticodon, a tRNA molecule can read its recognized mRNA codon and bring the corresponding amino acid to the growing chain ([link]).

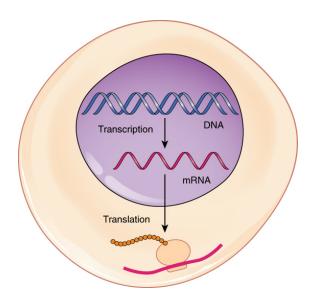
Translation from RNA to Protein



During translation, the mRNA transcript is "read" by a functional complex consisting of the ribosome and tRNA molecules. tRNAs bring the appropriate amino acids in sequence to the growing polypeptide chain by matching their anti-codons with codons on the mRNA strand.

Much like the processes of DNA replication and transcription, translation consists of three main stages: initiation, elongation, and termination. Initiation takes place with the binding of a ribosome to an mRNA transcript. The elongation stage involves the recognition of a tRNA anticodon with the next mRNA codon in the sequence. Once the anticodon and codon sequences are bound (remember, they are complementary base pairs), the tRNA presents its amino acid cargo and the growing polypeptide strand is attached to this next amino acid. This attachment takes place with the assistance of various enzymes and requires energy. The tRNA molecule then releases the mRNA strand, the mRNA strand shifts one codon over in the ribosome, and the next appropriate tRNA arrives with its matching anticodon. This process continues until the final codon on the mRNA is reached which provides a "stop" message that signals termination of translation and triggers the release of the complete, newly synthesized protein. Thus, a gene within the DNA molecule is transcribed into mRNA, which is then translated into a protein product ([link]).

From DNA to Protein: Transcription through Translation



Transcription within the cell nucleus produces an mRNA molecule, which is modified and then sent into the cytoplasm for translation.

The transcript is decoded into a protein with the help of a ribosome and tRNA molecules.

Commonly, an mRNA transcription will be translated simultaneously by several adjacent ribosomes. This increases the efficiency of protein synthesis. A single ribosome might translate an mRNA molecule in approximately one minute; so multiple ribosomes aboard a single transcript could produce multiple times the number of the same protein in the same minute. A polyribosome is a string of ribosomes translating a single mRNA strand.

N	Λ	t	Δ	•
Τ.4	v	U	C	•



Watch this <u>video</u> to learn about ribosomes. The ribosome binds to the mRNA molecule to start translation of its code into a protein. What happens to the small and large ribosomal subunits at the end of translation?

Chapter Review

DNA stores the information necessary for instructing the cell to perform all of its functions. Cells use the genetic code stored within DNA to build proteins, which ultimately determine the structure and function of the cell. This genetic code lies in the particular sequence of nucleotides that make up each gene along the DNA molecule. To "read" this code, the cell must perform two sequential steps. In the first step, transcription, the DNA code is converted into a RNA code. A molecule of messenger RNA that is complementary to a specific gene is synthesized in a process similar to DNA replication. The molecule of mRNA provides the code to synthesize a protein. In the process of translation, the mRNA attaches to a ribosome. Next, tRNA molecules shuttle the appropriate amino acids to the ribosome, one-by-one, coded by sequential triplet codons on the mRNA, until the protein is fully synthesized. When completed, the mRNA detaches from the ribosome, and the protein is released. Typically, multiple ribosomes attach to a single mRNA molecule at once such that multiple proteins can be manufactured from the mRNA concurrently.

Glossary

gene

functional length of DNA that provides the genetic information necessary to build a protein

gene expression

active interpretation of the information coded in a gene to produce a functional gene product

messenger RNA (mRNA)

nucleotide molecule that serves as an intermediate in the genetic code between DNA and protein

polypeptide

chain of amino acids linked by peptide bonds

proteome

full complement of proteins produced by a cell (determined by the cell's specific gene expression)

transcription

process of producing an mRNA molecule that is complementary to a particular gene of DNA

transfer RNA (tRNA)

molecules of RNA that serve to bring amino acids to a growing polypeptide strand and properly place them into the sequence

translation

process of producing a protein from the nucleotide sequence code of an mRNA transcript

OU Human Physiology: Cell Growth and Division By the end of this section, you will be able to:

- Describe the purpose of cell division
- Explain the importance of regulating cell division

So far in this chapter, you have read numerous times of the importance and prevalence of cell division. While there are a few cells in the body that do not undergo cell division (such as gametes, red blood cells, most neurons, and some muscle cells), most somatic cells divide regularly. A **somatic cell** is a general term for a body cell, and all human cells, except for the cells that produce eggs and sperm (which are referred to as germ cells), are somatic cells. Somatic cells contain *two* copies of each of their chromosomes (one copy received from each parent). A **homologous** pair of chromosomes is the two copies of a single chromosome found in each somatic cell. The human is a **diploid** organism, having 23 homologous pairs of chromosomes in each of the somatic cells. The condition of having pairs of chromosomes is known as diploidy.

Cells in the body replace themselves over the lifetime of a person. For example, the cells lining the gastrointestinal tract must be frequently replaced when constantly "worn off" by the movement of food through the gut. But what triggers a cell to divide, and how does it prepare for and complete cell division? The **cell cycle** is the sequence of events in the life of the cell from the moment it is created at the end of a previous cycle of cell division until it then divides itself, generating two new cells.

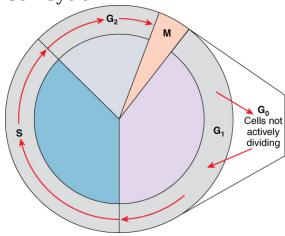
The Cell Cycle

One "turn" or cycle of the cell cycle consists of two general phases: interphase, followed by mitosis and cytokinesis. Interphase is the period of the cell cycle during which the cell is not dividing. The majority of cells are in interphase most of the time. **Mitosis** is the division of genetic material, during which the cell nucleus breaks down and two new, fully functional, nuclei are formed. **Cytokinesis** divides the cytoplasm into two distinctive cells.

Interphase

A cell grows and carries out all normal metabolic functions and processes in a period called G_1 ([link]). G_1 phase (gap 1 phase) is the first gap, or growth phase in the cell cycle. For cells that will divide again, G_1 is followed by replication of the DNA, during the S phase. The S phase (synthesis phase) is period during which a cell replicates its DNA.

Cell Cycle



The two major phases of the cell cycle include mitosis (cell division), and interphase, when the cell grows and performs all of its normal functions. Interphase is further subdivided into G_1 , S, and G_2 phases.

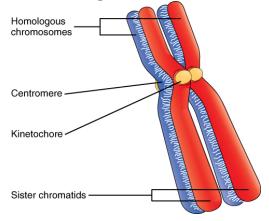
After the synthesis phase, the cell proceeds through the G_2 phase. The G_2 phase is a second gap phase, during which the cell continues to grow and makes the necessary preparations for mitosis. Between G_1 , S, and G_2 phases, cells will vary the most in their duration of the G_1 phase. It is here that a cell might spend a couple of hours, or many days. The S phase typically lasts between S_1 0 hours and the G_2 phase approximately S_2 hours. In contrast to these phases, the S_3 0 phase is a resting phase of the cell cycle.

Cells that have temporarily stopped dividing and are resting (a common condition) and cells that have permanently ceased dividing (like nerve cells) are said to be in G_0 .

The Structure of Chromosomes

Billions of cells in the human body divide every day. During the synthesis phase (S, for DNA synthesis) of interphase, the amount of DNA within the cell precisely doubles. Therefore, after DNA replication but before cell division, each cell actually contains *two* copies of each chromosome. Each copy of the chromosome is referred to as a sister chromatid and is physically bound to the other copy. The centromere is the structure that attaches one sister chromatid to another. Because a human cell has 46 chromosomes, during this phase, there are 92 chromatids (46×2) in the cell. Make sure not to confuse the concept of a pair of chromatids (one chromosome and its exact copy attached during mitosis) and a homologous pair of chromosomes (two paired chromosomes which were inherited separately, one from each parent) ([link]).

A Homologous Pair of Chromosomes with their Attached Sister Chromatids



The red and blue colors correspond to a homologous pair of chromosomes. Each member of the pair was separately inherited from

one parent. Each chromosome in the homologous pair is also bound to an identical sister chromatid, which is produced by DNA replication, and results in the familiar "X" shape.

Mitosis and Cytokinesis

The mitotic phase of the cell typically takes between 1 and 2 hours. During this phase, a cell undergoes two major processes. First, it completes mitosis, during which the contents of the nucleus are equitably pulled apart and distributed between its two halves. Cytokinesis then occurs, dividing the cytoplasm and cell body into two new cells. Mitosis is divided into four major stages that take place after interphase ([link]) and in the following order: prophase, metaphase, anaphase, and telophase. The process is then followed by cytokinesis.

Cell Division: Mitosis Followed by Cytokinesis

Prophase	Prometaphase	Metaphase	Anaphase	Telophase	Cytokinesis
		X			
Chromosomes condense and become visible Spindle fibers emerge from the centrosomes Nuclear envelope breaks down Centrosomes move toward opposite poles	Chromosomes continue to condense Kinetochores appear at the centromeres Mitotic spindle microtubules attach to kinetochores	Chromosomes are lined up at the metaphase plate Each sister chromatid is attached to a spindle fiber originating from opposite poles	Centromeres split in two Sister chromatids (now called chromosomes) are pulled toward opposite poles Certain spindle fibers begin to elongate the cell	Chromosomes arrive at opposite poles and begin to decondense Nuclear envelope material surrounds each set of chromosomes The mitotic spindle breaks down Spindle fibers continue to push poles apart	Animal cells: a cleavage furrow separates the daughter cells Plant cells: a cell plate, the precursor to a new cell wall, separates the daughter cells
<u>5 µm</u>	5 μm	5 μm	<u>5 μm</u>	5 μm	5 μm
		I MITOSIS			

The stages of cell division oversee the separation of identical genetic material into two new nuclei, followed by the division of the cytoplasm.

Prophase is the first phase of mitosis, during which the loosely packed chromatin coils and condenses into visible chromosomes. During prophase, each chromosome becomes visible with its identical partner attached, forming the familiar X-shape of sister chromatids. The nucleolus disappears early during this phase, and the nuclear envelope also disintegrates.

A major occurrence during prophase concerns a very important structure that contains the origin site for microtubule growth. Recall the cellular structures called centrioles that serve as origin points from which microtubules extend. These tiny structures also play a very important role during mitosis. A centrosome is a pair of centrioles together. The cell contains two centrosomes side-by-side, which begin to move apart during prophase. As the centrosomes migrate to two different sides of the cell, microtubules begin to extend from each like long fingers from two hands extending toward each other. The mitotic spindle is the structure composed of the centrosomes and their emerging microtubules.

Near the end of prophase there is an invasion of the nuclear area by microtubules from the mitotic spindle. The nuclear membrane has disintegrated, and the microtubules attach themselves to the centromeres that adjoin pairs of sister chromatids. The kinetochore is a protein structure on the centromere that is the point of attachment between the mitotic spindle and the sister chromatids. This stage is referred to as late prophase or "prometaphase" to indicate the transition between prophase and metaphase.

Metaphase is the second stage of mitosis. During this stage, the sister chromatids, with their attached microtubules, line up along a linear plane in the middle of the cell. A metaphase plate forms between the centrosomes that are now located at either end of the cell. The metaphase plate is the name for the plane through the center of the spindle on which the sister chromatids are positioned. The microtubules are now poised to pull apart the sister chromatids and bring one from each pair to each side of the cell.

Anaphase is the third stage of mitosis. Anaphase takes place over a few minutes, when the pairs of sister chromatids are separated from one another, forming individual chromosomes once again. These chromosomes are pulled to opposite ends of the cell by their kinetochores, as the microtubules shorten. Each end of the cell receives one partner from each pair of sister chromatids, ensuring that the two new daughter cells will contain identical genetic material.

Telophase is the final stage of mitosis. Telophase is characterized by the formation of two new daughter nuclei at either end of the dividing cell. These newly formed nuclei surround the genetic material, which uncoils such that the chromosomes return to loosely packed chromatin. Nucleoli also reappear within the new nuclei, and the mitotic spindle breaks apart, each new cell receiving its own complement of DNA, organelles,

membranes, and centrioles. At this point, the cell is already beginning to split in half as cytokinesis begins.

The cleavage furrow is a contractile band made up of microfilaments that forms around the midline of the cell during cytokinesis. (Recall that microfilaments consist of actin.) This contractile band squeezes the two cells apart until they finally separate. Two new cells are now formed. One of these cells (the "stem cell") enters its own cell cycle; able to grow and divide again at some future time. The other cell transforms into the functional cell of the tissue, typically replacing an "old" cell there.

Imagine a cell that completed mitosis but never underwent cytokinesis. In some cases, a cell may divide its genetic material and grow in size, but fail to undergo cytokinesis. This results in larger cells with more than one nucleus. Usually this is an unwanted aberration and can be a sign of cancerous cells.

Cell Cycle Control

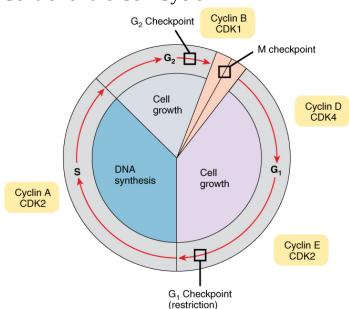
A very elaborate and precise system of regulation controls direct the way cells proceed from one phase to the next in the cell cycle and begin mitosis. The control system involves molecules within the cell as well as external triggers. These internal and external control triggers provide "stop" and "advance" signals for the cell. Precise regulation of the cell cycle is critical for maintaining the health of an organism, and loss of cell cycle control can lead to cancer.

Mechanisms of Cell Cycle Control

As the cell proceeds through its cycle, each phase involves certain processes that must be completed before the cell should advance to the next phase. A checkpoint is a point in the cell cycle at which the cycle can be signaled to move forward or stopped. At each of these checkpoints, different varieties of molecules provide the stop or go signals, depending on certain conditions within the cell. A cyclin is one of the primary classes of cell cycle control molecules ([link]). A cyclin-dependent kinase (CDK) is

one of a group of molecules that work together with cyclins to determine progression past cell checkpoints. By interacting with many additional molecules, these triggers push the cell cycle forward unless prevented from doing so by "stop" signals, if for some reason the cell is not ready. At the G_1 checkpoint, the cell must be ready for DNA synthesis to occur. At the G_2 checkpoint the cell must be fully prepared for mitosis. Even during mitosis, a crucial stop and go checkpoint in metaphase ensures that the cell is fully prepared to complete cell division. The metaphase checkpoint ensures that all sister chromatids are properly attached to their respective microtubules and lined up at the metaphase plate before the signal is given to separate them during anaphase.

Control of the Cell Cycle



Cells proceed through the cell cycle under the control of a variety of molecules, such as cyclins and cyclindependent kinases. These control molecules determine whether or not the cell is prepared to move into the following stage.

The Cell Cycle Out of Control: Implications

Most people understand that cancer or tumors are caused by abnormal cells that multiply continuously. If the abnormal cells continue to divide unstopped, they can damage the tissues around them, spread to other parts of the body, and eventually result in death. In healthy cells, the tight regulation mechanisms of the cell cycle prevent this from happening, while failures of cell cycle control can cause unwanted and excessive cell division. Failures of control may be caused by inherited genetic abnormalities that compromise the function of certain "stop" and "go" signals. Environmental insult that damages DNA can also cause dysfunction in those signals. Often, a combination of both genetic predisposition and environmental factors lead to cancer.

The process of a cell escaping its normal control system and becoming cancerous may actually happen throughout the body quite frequently. Fortunately, certain cells of the immune system are capable of recognizing cells that have become cancerous and destroying them. However, in certain cases the cancerous cells remain undetected and continue to proliferate. If the resulting tumor does not pose a threat to surrounding tissues, it is said to be benign and can usually be easily removed. If capable of damage, the tumor is considered malignant and the patient is diagnosed with cancer.

Note:

Homeostatic Imbalances

Cancer Arises from Homeostatic Imbalances

Cancer is an extremely complex condition, capable of arising from a wide variety of genetic and environmental causes. Typically, mutations or aberrations in a cell's DNA that compromise normal cell cycle control systems lead to cancerous tumors. Cell cycle control is an example of a homeostatic mechanism that maintains proper cell function and health. While progressing through the phases of the cell cycle, a large variety of intracellular molecules provide stop and go signals to regulate movement forward to the next phase. These signals are maintained in an intricate balance so that the cell only proceeds to the next phase when it is ready. This homeostatic control of the cell cycle can be thought of like a car's

cruise control. Cruise control will continually apply just the right amount of acceleration to maintain a desired speed, unless the driver hits the brakes, in which case the car will slow down. Similarly, the cell includes molecular messengers, such as cyclins, that push the cell forward in its cycle.

In addition to cyclins, a class of proteins that are encoded by genes called proto-oncogenes provide important signals that regulate the cell cycle and move it forward. Examples of proto-oncogene products include cell-surface receptors for growth factors, or cell-signaling molecules, two classes of molecules that can promote DNA replication and cell division. In contrast, a second class of genes known as tumor suppressor genes sends stop signals during a cell cycle. For example, certain protein products of tumor suppressor genes signal potential problems with the DNA and thus stop the cell from dividing, while other proteins signal the cell to die if it is damaged beyond repair. Some tumor suppressor proteins also signal a sufficient surrounding cellular density, which indicates that the cell need not presently divide. The latter function is uniquely important in preventing tumor growth: normal cells exhibit a phenomenon called "contact inhibition;" thus, extensive cellular contact with neighboring cells causes a signal that stops further cell division.

These two contrasting classes of genes, proto-oncogenes and tumor suppressor genes, are like the accelerator and brake pedal of the cell's own "cruise control system," respectively. Under normal conditions, these stop and go signals are maintained in a homeostatic balance. Generally speaking, there are two ways that the cell's cruise control can lose control: a malfunctioning (overactive) accelerator, or a malfunctioning (underactive) brake. When compromised through a mutation, or otherwise altered, proto-oncogenes can be converted to oncogenes, which produce oncoproteins that push a cell forward in its cycle and stimulate cell division even when it is undesirable to do so. For example, a cell that should be programmed to self-destruct (a process called apoptosis) due to extensive DNA damage might instead be triggered to proliferate by an oncoprotein. On the other hand, a dysfunctional tumor suppressor gene may fail to provide the cell with a necessary stop signal, also resulting in unwanted cell division and proliferation.

A delicate homeostatic balance between the many proto-oncogenes and tumor suppressor genes delicately controls the cell cycle and ensures that only healthy cells replicate. Therefore, a disruption of this homeostatic balance can cause aberrant cell division and cancerous growths.

Note:



Visit this <u>link</u> to learn about mitosis. Mitosis results in two identical diploid cells. What structures forms during prophase?

Chapter Review

The life of cell consists of stages that make up the cell cycle. After a cell is born, it passes through an interphase before it is ready to replicate itself and produce daughter cells. This interphase includes two gap phases (G_1 and G_2), as well as an S phase, during which its DNA is replicated in preparation for cell division. The cell cycle is under precise regulation by chemical messengers both inside and outside the cell that provide "stop" and "go" signals for movement from one phase to the next. Failures of these signals can result in cells that continue to divide uncontrollably, which can lead to cancer.

Once a cell has completed interphase and is ready for cell division, it proceeds through four separate stages of mitosis (prophase, metaphase, anaphase, and telophase). Telophase is followed by the division of the cytoplasm (cytokinesis), which generates two daughter cells. This process takes place in all normally dividing cells of the body except for the germ cells that produce eggs and sperm.

Glossary

cell cycle

life cycle of a single cell, from its birth until its division into two new daughter cells

cytokinesis

final stage in cell division, where the cytoplasm divides to form two separate daughter cells

diploid

condition marked by the presence of a double complement of genetic material (two sets of chromosomes, one set inherited from each of two parents)

homologous

describes two copies of the same chromosome (not identical), one inherited from each parent

mitosis

division of genetic material, during which the cell nucleus breaks down and two new, fully functional, nuclei are formed

somatic cell

all cells of the body excluding gamete cells

OU Human Physiology: Cellular Differentiation By the end of this section, you will be able to:

- Discuss how the generalized cells of a developing embryo or the stem cells of an adult organism become differentiated into specialized cells
- Distinguish between the categories of stem cells

How does a complex organism such as a human develop from a single cell—a fertilized egg—into the vast array of cell types such as nerve cells, muscle cells, and epithelial cells that characterize the adult? Throughout development and adulthood, the process of cellular differentiation leads cells to assume their final morphology and physiology. Differentiation is the process by which unspecialized cells become specialized to carry out distinct functions.

Stem Cells

A **stem cell** is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate ([link]).

The first embryonic cells that arise from the division of the zygote are the ultimate stem cells; these stems cells are described as **totipotent** because they have the potential to differentiate into any of the cells needed to enable an organism to grow and develop.

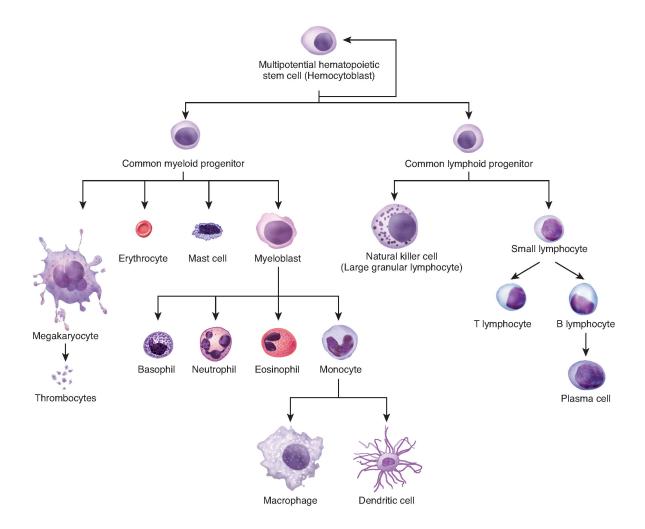
The embryonic cells that develop from totipotent stem cells and are precursors to the fundamental tissue layers of the embryo are classified as pluripotent. A **pluripotent** stem cell is one that has the potential to differentiate into any type of human tissue but cannot support the full development of an organism. These cells then become slightly more specialized, and are referred to as multipotent cells.

A **multipotent** stem cell has the potential to differentiate into different types of cells within a given cell lineage or small number of lineages, such as a red blood cell or white blood cell.

Finally, multipotent cells can become further specialized oligopotent cells. An **oligopotent** stem cell is limited to becoming one of a few different cell types. In contrast, an **unipotent** cell is fully specialized and can only reproduce to generate more of its own specific cell type.

Stem cells are unique in that they can also continually divide and regenerate new stem cells instead of further specializing. There are different stem cells present at different stages of a human's life. They include the embryonic stem cells of the embryo, fetal stem cells of the fetus, and adult stem cells in the adult. One type of adult stem cell is the epithelial stem cell, which gives rise to the keratinocytes in the multiple layers of epithelial cells in the epidermis of skin. Adult bone marrow has three distinct types of stem cells: hematopoietic stem cells, which give rise to red blood cells, white blood cells, and platelets ([link]; we will revisit this concept of hematopoiesis at a later time); endothelial stem cells, which give rise to the endothelial cell types that line blood and lymph vessels; and mesenchymal stem cells, which give rise to the different types of muscle cells.

Hematopoiesis



The process of hematopoiesis involves the differentiation of multipotent cells into blood and immune cells. The multipotent hematopoietic stem cells give rise to many different cell types, including the cells of the immune system and red blood cells.

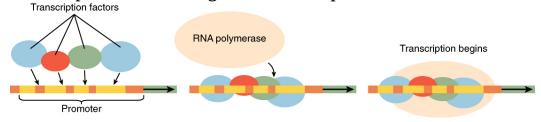
Differentiation

When a cell differentiates (becomes more specialized), it may undertake major changes in its size, shape, metabolic activity, and overall function. Because all cells in the body, beginning with the fertilized egg, contain the same DNA, how do the different cell types come to be so different? The answer is analogous to a movie script. The different actors in a movie all

read from the same script, however, they are each only reading their own part of the script. Similarly, all cells contain the same full complement of DNA, but each type of cell only "reads" the portions of DNA that are relevant to its own function. In biology, this is referred to as the unique genetic expression of each cell.

In order for a cell to differentiate into its specialized form and function, it need only manipulate those genes (and thus those proteins) that will be expressed, and not those that will remain silent. The primary mechanism by which genes are turned "on" or "off" is through transcription factors. A transcription factor is one of a class of proteins that bind to specific genes on the DNA molecule and either promote or inhibit their transcription ([link]).

Transcription Factors Regulate Gene Expression



While each body cell contains the organism's entire genome, different cells regulate gene expression with the use of various transcription factors. Transcription factors are proteins that affect the binding of RNA polymerase to a particular gene on the DNA molecule.

Note:

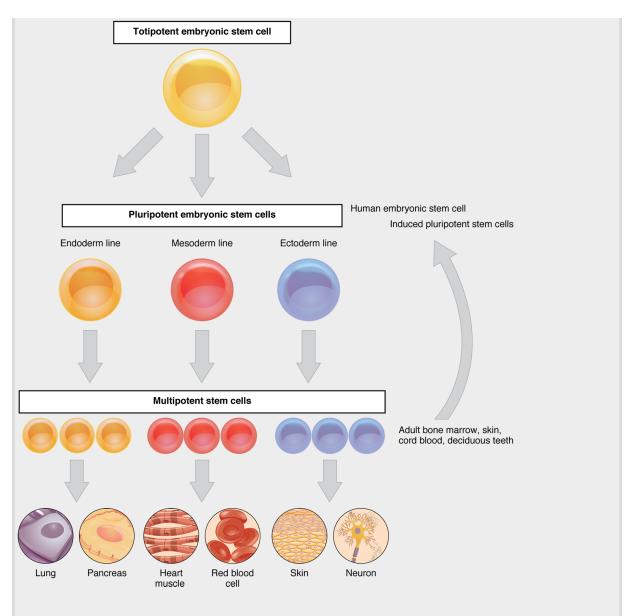
Everyday Connection **Stem Cell Research**

Stem cell research aims to find ways to use stem cells to regenerate and repair cellular damage. Over time, most adult cells undergo the wear and tear of aging and lose their ability to divide and repair themselves. Stem cells do not display a particular morphology or function. Adult stem cells,

which exist as a small subset of cells in most tissues, keep dividing and can differentiate into a number of specialized cells generally formed by that tissue. These cells enable the body to renew and repair body tissues. The mechanisms that induce a non-differentiated cell to become a specialized cell are poorly understood. In a laboratory setting, it is possible to induce stem cells to differentiate into specialized cells by changing the physical and chemical conditions of growth. Several sources of stem cells are used experimentally and are classified according to their origin and potential for differentiation. Human embryonic stem cells (hESCs) are extracted from embryos and are pluripotent. The adult stem cells that are present in many organs and differentiated tissues, such as bone marrow and skin, are multipotent, being limited in differentiation to the types of cells found in those tissues. The stem cells isolated from umbilical cord blood are also multipotent, as are cells from deciduous teeth (baby teeth). Researchers have recently developed induced pluripotent stem cells (iPSCs) from mouse and human adult stem cells. These cells are genetically reprogrammed multipotent adult cells that function like embryonic stem cells; they are capable of generating cells characteristic of all three germ layers.

Because of their capacity to divide and differentiate into specialized cells, stem cells offer a potential treatment for diseases such as diabetes and heart disease ([link]). Cell-based therapy refers to treatment in which stem cells induced to differentiate in a growth dish are injected into a patient to repair damaged or destroyed cells or tissues. Many obstacles must be overcome for the application of cell-based therapy. Although embryonic stem cells have a nearly unlimited range of differentiation potential, they are seen as foreign by the patient's immune system and may trigger rejection. Also, the destruction of embryos to isolate embryonic stem cells raises considerable ethical and legal questions.

Stem Cells



The capacity of stem cells to differentiate into specialized cells make them potentially valuable in therapeutic applications designed to replace damaged cells of different body tissues.

In contrast, adult stem cells isolated from a patient are not seen as foreign by the body, but they have a limited range of differentiation. Some individuals bank the cord blood or deciduous teeth of their child, storing away those sources of stem cells for future use, should their child need it. Induced pluripotent stem cells are considered a promising advance in the field because using them avoids the legal, ethical, and immunological pitfalls of embryonic stem cells.

Glossary

multipotent

describes the condition of being able to differentiate into different types of cells within a given cell lineage or small number of lineages, such as a red blood cell or white blood cell

oligopotent

describes the condition of being more specialized than multipotency; the condition of being able to differentiate into one of a few possible cell types

pluripotent

describes the condition of being able to differentiate into a large variety of cell types

stem cell

cell that is oligo-, multi-, or pleuripotent that has the ability to produce additional stem cells rather than becoming further specialized

totipotent

embryonic cells that have the ability to differentiate into any type of cell and organ in the body

unipotent

describes the condition of being committed to a single specialized cell type

OU Human Physiology: The Cell Membrane Introduction

Note:

Chapter Onjectives

By the end of this chapter you should be able to:

- Compare and contrast extracellular and intracellular fluid in terms of composition and importance for homeostasis
- Describe the structure and function of the cell membrane including its regulation of materials into and out of the cell
- Compare and contrast the various types of membrane transport including bulk (vesicular) transport
- Explain chemical and electrical gradients in terms of solute transport
- Relate knowledge of membrane transport to epithelial transport in the human body
- Solve membrane transport problems

Despite differences in structure and function, all living cells in multicellular organisms have a surrounding cell membrane. As the outer layer of your skin separates your body from its environment, the cell membrane (also known as the plasma membrane) separates the inner contents of a cell from its exterior environment. This cell membrane provides a protective barrier around the cell and regulates which materials can pass in or out.

OU Human Physiology: Structure and Composition of the Cell Membrane By the end of this section, you will be able to:

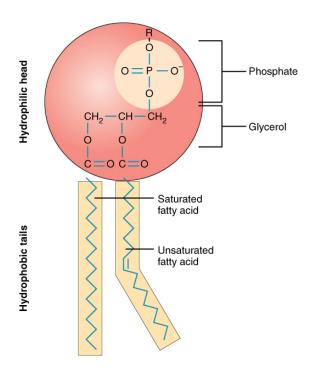
- Describe the molecular components that make up the cell membrane
- Explain the major features and properties of the cell membrane
- Differentiate between materials that can and cannot diffuse through the lipid bilayer
- Compare and contrast different types of passive transport with active transport, providing examples of each

Structure and Composition of the Cell Membrane

The **cell membrane** is an extremely pliable structure composed primarily of back-to-back phospholipids (a "bilayer"). Cholesterol is also present, which contributes to the fluidity of the membrane, and there are various proteins embedded within the membrane that have a variety of functions.

A single phospholipid molecule has a phosphate group on one end, called the "head," and two side-by-side chains of fatty acids that make up the lipid tails ([link]). The phosphate group is negatively charged, making the head polar and hydrophilic—or "water loving." A hydrophilic molecule (or region of a molecule) is one that is attracted to water. The phosphate heads are thus attracted to the water molecules of both the extracellular and intracellular environments. The lipid tails, on the other hand, are uncharged, or nonpolar, and are hydrophobic—or "water fearing." A hydrophobic molecule (or region of a molecule) repels and is repelled by water. Some lipid tails consist of saturated fatty acids and some contain unsaturated fatty acids. This combination adds to the fluidity of the tails that are constantly in motion. Phospholipids are thus amphipathic molecules. An **amphipathic** molecule is one that contains both a hydrophilic and a hydrophobic region. In fact, soap works to remove oil and grease stains because it has amphipathic properties. The hydrophilic portion can dissolve in water while the hydrophobic portion can trap grease in micelles that then can be washed away.

Phospholipid Structure

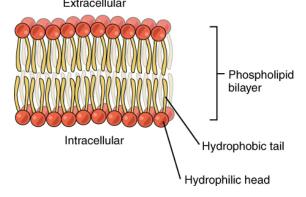


A phospholipid molecule consists of a polar phosphate "head," which is hydrophilic and a non-polar lipid "tail," which is hydrophobic.
Unsaturated fatty acids result in kinks in the hydrophobic tails.

The cell membrane consists of two adjacent layers of phospholipids. The lipid tails of one layer face the lipid tails of the other layer, meeting at the interface of the two layers. The phospholipid heads face outward, one layer exposed to the interior of the cell and one layer exposed to the exterior ([link]). Because the phosphate groups are polar and hydrophilic, they are attracted to water in the intracellular fluid. Intracellular fluid (ICF) is the fluid interior of the cell. The phosphate groups are also attracted to the extracellular fluid. Extracellular fluid (ECF) is the fluid environment outside the enclosure of the cell membrane. Interstitial fluid (IF) is the term given to extracellular fluid that is present outside the blood and bathes

the cells. The plasma is the liquid part of the extracellular fluid that is found in the blood. Because the lipid tails are hydrophobic, they meet in the inner region of the membrane, excluding watery intracellular and extracellular fluid from this space. The cell membrane has many proteins, as well as other lipids (such as cholesterol), that are associated with the phospholipid bilayer. An important feature of the membrane is that it remains fluid; the lipids and proteins in the cell membrane are not rigidly locked in place.

Phospolipid Bilayer



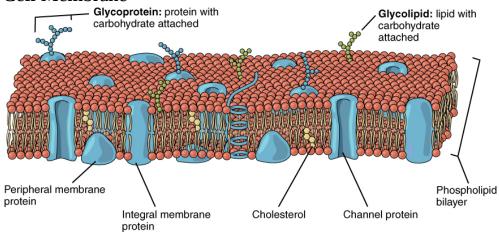
The phospholipid bilayer consists of two adjacent sheets of phospholipids, arranged tail to tail. The hydrophobic tails associate with one another, forming the interior of the membrane. The polar heads contact the fluid inside and outside of the cell.

Membrane Proteins

The lipid bilayer forms the basis of the cell membrane, but it is peppered throughout with various proteins. Two different types of proteins that are commonly associated with the cell membrane are the integral proteins and peripheral proteins ([link]). As its name suggests, an **integral protein** is a

protein that is physically connected to the membrane. Some integral proteins are called transmembrane proteins because they contact both the ECF and ICF. Examples of transmembrane proteins include channels and carrier proteins. A **channel protein** is an example of an integral protein that selectively allows particular materials, such as certain ions, to pass into or out of the cell, like iced tea through a drinking straw. A **carrier protein** is also an example of an integral protein, but this protein moves particular solutes to the opposite side of the membrane when the solutes bind to the carrier protein, which then allows the solute to pass to the other side by undergoing a conformational change. Both channels and carrier proteins illustrate specificity ensuring the proteins only transport one type or family of molecules.

Cell Membrane



The cell membrane of the cell is a phospholipid bilayer containing many different molecular components, including proteins and cholesterol, some with carbohydrate groups attached.

Other integral proteins are only located on one side of the membrane. These include enzymes, receptors, and glycoproteins and glycolipids. **Enzymes** facilitate chemical reactions. We will return to the concept of enzymes at a later time. A **receptor** is a type of recognition protein that can selectively bind a specific molecule outside the cell, and this binding induces a chemical reaction within the cell. A **ligand** is the specific molecule that

binds to and activates a receptor. Some integral proteins serve dual roles as both a receptor and an ion channel. One example of a receptor-ligand interaction is the receptors on nerve cells that bind neurotransmitters, such as dopamine. When a dopamine molecule binds to a dopamine receptor protein, a channel within the transmembrane protein opens to allow certain ions to flow into the cell.

Some integral membrane proteins are glycoproteins and glycolipids. A **glycoprotein** is a protein that has carbohydrate molecules attached, while a **glycolipid** is a lipid that has a carbohydrate attached. Both glycoproteins and glycolipids extend into the extracellular matrix. The attached carbohydrate tags on both glycolipids and glycoproteins aid in cell recognition. The carbohydrates that extend from membrane proteins and even from some membrane lipids collectively form the glycocalyx. The **glycocalyx** is a fuzzy-appearing coating around the cell formed from glycoproteins and glycolipids attached to the cell membrane. The glycocalyx can have various roles. For example, it may have molecules that allow the cell to bind to another cell, it may contain receptors for hormones, or it might have enzymes to break down nutrients. The glycocalyces found in a person's body are products of that person's genetic makeup. They give each of the individual's trillions of cells the "identity" of belonging in the person's body. This identity is the primary way that a person's immune defense cells "know" not to attack the person's own body cells, but it also is the reason organs donated by another person might be rejected.

Peripheral proteins are not strongly bound to the membrane and can be found on the inner or outer surface of the lipid bilayer. Additionally, they can also be attached to the internal or external surface of an integral protein. Many of these peripheral proteins makeup the cytoskeleton of the cell.

Membrane lipids

There are two types of lipids that help form the plasma membrane, the phospholipids and cholesterol. We have already spent much needed attention on the phospholipids so here we will briefly concentrate on cholesterol. Cholesterol molecules are associated with the fatty acid tails of

the phospholipids. Their role is to help the plasma membrane retain its fluidity by preventing the phospholipids from packing close together.

Chapter Review

The cell membrane provides a barrier around the cell, separating its internal components from the extracellular environment. It is composed of a phospholipid bilayer, with hydrophobic lipid 'tails' and hydrophilic 'heads.' Various membrane proteins are scattered throughout the bilayer, both inserted within it and attached to it peripherally. The cell membrane is selectively permeable, allowing only a limited number of materials to diffuse through its lipid bilayer.

Glossary

amphipathic

describes a molecule that exhibits a difference in polarity between its two ends, resulting in a difference in water solubility

carrier protein

a transmembrane protein that requires binding of a solute that elicits a conformational change to allow solute movement across the cell membrane

cell membrane

membrane surrounding all animal cells, composed of a lipid bilayer interspersed with various molecules; also known as plasma membrane

channel protein

membrane-spanning protein that has an inner pore which allows the passage of one or more substances

enzyme

most often a protein that facilitates a chemical reaction

extracellular fluid (ECF)

fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluid found in other reservoirs in the body

glycocalyx

coating of sugar molecules that surrounds the cell membrane

glycolipid

a membrane carbohydrate with a lipid attached that is important in cell recognition and holding cells together

glycoprotein

protein that has one or more carbohydrates attached

hydrophilic

describes a substance or structure attracted to water

hydrophobic

describes a substance or structure repelled by water

integral protein

membrane-associated protein that spans the entire width of the lipid bilayer

interstitial fluid (IF)

fluid in the small spaces between cells not contained within blood vessels

intracellular fluid (ICF)

fluid in the cytosol of cells

ligand

molecule that binds with specificity to a specific receptor molecule

plasma

part of the extracellular fluid that bathes the cells in the blood

peripheral protein

membrane-associated protein that does not span the width of the lipid bilayer, but is attached peripherally to integral proteins, membrane lipids, or other components of the membrane

receptor

protein molecule that contains a binding site for another specific molecule (called a ligand)

OU Human Physiology: Introduction to Membrane Transport By the end of this section, you will be able to:

- Explain the importance of membrane transport
- Determine the net direction of solute movement via chemical and electrical gradients
- Categorize common solutes in terms of membrane permeability
- Explain the importance of membrane transport
- Categorize common solutes in terms of type of membrane transport
- Compare and contrast the various types of membrane transport including bulk (vesicular) transport
- Infer knowledge of membrane transport to epithelial transport

Despite differences in structure and function, all living cells in multicellular organisms have a surrounding cell membrane. As the outer layer of your skin separates your body from its environment, the cell membrane (also known as the plasma membrane) separates the inner contents of a cell from its exterior environment. This cell membrane provides a protective barrier around the cell and regulates which materials can pass in or out.

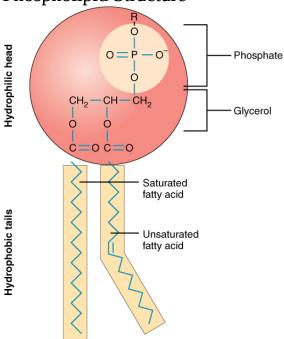
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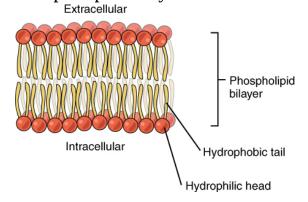


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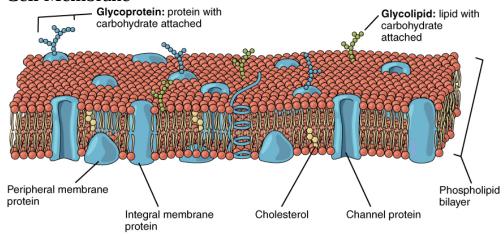


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cholesterol. Cholesterol molecules are associated with the fatty acid tails of the phospholipids. Their role is to help the plasma membrane retain its fluidity by preventing the phospholipids from packing close together.

Driving Forces for Solute Movement

Random thermal motion (Brownian movement) says "molecules are always moving" and every time these molecules collide they generate energy which forces those molecules to move from a higher energy state to a lower energy state. Remember bumper cars? Here's a picture to remind you of what those are ([link]). If bumper cars were the equivalent of molecules, and two cars collided, would that generate energy? Would that force the cars to move? The answer is yes, when the cars collide that generates energy which moves the cars from higher to lower energy. There are three types of driving forces that cause solutes to move: chemical, electrical, and electrochemical.

Bumper car fun

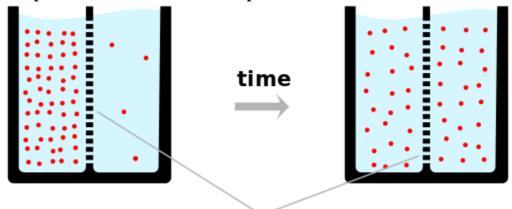


A reminder of what a bumper car attraction at an amusement park looks like. Photo by Anneli Salo.

The chemical driving force is based on the concentration gradient. A concentration gradient (also called a chemical gradient) is the difference in

concentration of a substance across the cell membrane. Molecules will spread/diffuse from where they are more concentrated to where they are less concentrated until they are equally distributed in space (equilibrium). When molecules move in this way, they are said to move down their concentration gradient ([link]).

Simple diffusion across a semipermeable membrane



semipermeable membrane

Molecules move down their concentration gradient until they are equally distributed in space.

The electrical driving force can also affect the movement of molecules across the membrane, which is dependent on the electrical gradient. An electrical gradient is a difference in electrical charge across the cell membrane. Since this gradient is dependent on electrical charges, the electrical gradient is only relevant to solutes that are charged. As a reminder, remember that like charges repel and opposite charges attract. In the case of nerve cells, for example, the electrical gradient exists between the inside and outside of the cell, with the inside being negatively-charged relative to the outside. For example, under normal conditions, the ICF has a net negative charge while the ECF has a net positive charge. If a cation was introduced into the ECF would there be a driving force pushing the cation into the ICF? The answer is yes, since a cation is positively charged and the ICF has a net negative charge, the cation will move into the cell.

Transport across the Cell Membrane

One of the great wonders of the cell membrane is its ability to regulate the concentration of substances inside the cell. These substances include ions such as Ca⁺⁺, Na⁺, K⁺, and Cl⁻; nutrients including sugars, fatty acids, and amino acids; and waste products, particularly carbon dioxide (CO₂), which must leave the cell.

The membrane's lipid bilayer structure provides the first level of control. The phospholipids are tightly packed together, and the membrane has a hydrophobic interior. This structure causes the membrane to be selectively permeable. A membrane that has **selective permeability** allows only substances meeting certain criteria to pass through it unaided. In the case of the cell membrane, only relatively small, nonpolar materials can move through the lipid bilayer (remember, the lipid tails of the membrane are nonpolar). Some examples of these are other lipids, oxygen and carbon dioxide gases, and alcohol. However, water-soluble materials—like glucose, amino acids, and electrolytes—need some assistance to cross the membrane because they are repelled by the hydrophobic tails of the phospholipid bilayer. All substances that move through the membrane do so by one of two general methods, which are categorized based on whether or not energy is required. **Passive transport** is the movement of substances across the membrane without the expenditure of cellular energy. In contrast, active transport is the movement of substances across the membrane using energy.

Passive Transport

Simple diffusion is the movement of particles from an area of higher concentration to an area of lower concentration. A couple of common examples will help to illustrate this concept. Imagine being inside a closed bathroom. If a bottle of perfume were sprayed, the scent molecules would naturally diffuse from the spot where they left the bottle to all corners of the bathroom, and this diffusion would go on until no more concentration gradient remains. Another example is a spoonful of sugar placed in a cup of tea. Eventually the sugar will diffuse throughout the tea until no

concentration gradient remains. In both cases, if the room is warmer or the tea hotter, diffusion occurs even faster as the molecules are bumping into each other and spreading out faster than at cooler temperatures. Having an internal body temperature around 98.6° F thus also aids in diffusion of particles within the body.

Note:



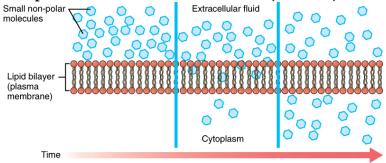
Visit this <u>link</u> to see diffusion and how it is propelled by the kinetic energy of molecules in solution. How does temperature affect diffusion rate, and why?

Whenever a substance exists in greater concentration on one side of a semipermeable membrane, such as the cell membranes, any substance that can move down its concentration gradient across the membrane will do so. Consider substances that can easily diffuse through the lipid bilayer of the cell membrane, such as the gases oxygen (O_2) and CO_2 . O_2 generally diffuses into cells because it is more concentrated outside of them, and CO_2 typically diffuses out of cells because it is more concentrated inside of them. Neither of these examples requires any energy on the part of the cell, and therefore they use passive transport to move across the membrane.

Before moving on, you need to review the gases that can diffuse across a cell membrane. Because cells rapidly use up oxygen during metabolism, there is typically a lower concentration of O_2 inside the cell than outside. As a result, oxygen will diffuse from the interstitial fluid directly through the lipid bilayer of the membrane and into the cytoplasm within the cell. On the other hand, because cells produce CO_2 as a byproduct of metabolism, CO_2

concentrations rise within the cytoplasm; therefore, CO₂ will move from the cell through the lipid bilayer and into the interstitial fluid, where its concentration is lower. This mechanism of molecules spreading from where they are more concentrated to where they are less concentrated is a form of passive transport called simple diffusion ([link]).

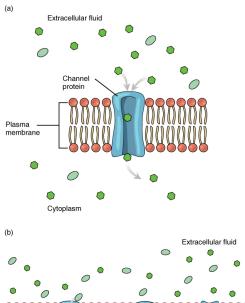
Simple Diffusion across the Cell (Plasma) Membrane

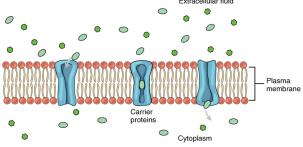


The structure of the lipid bilayer allows only small, non-polar substances such as oxygen and carbon dioxide to pass through the cell membrane, down their concentration gradient, by simple diffusion.

Solutes dissolved in water on either side of the cell membrane will tend to diffuse down their concentration gradients, but because most substances cannot pass freely through the lipid bilayer of the cell membrane, their movement is restricted to transmembrane proteins. **Facilitated diffusion** is the diffusion process used for those substances that cannot cross the lipid bilayer due to their size and/or polarity ([link]). A common example of facilitated diffusion is the movement of glucose into the cell, where it is used to make ATP. Although glucose can be more concentrated outside of a cell, it cannot cross the lipid bilayer via simple diffusion because it is both large and polar. To resolve this, a specialized carrier protein called the glucose transporter will transfer glucose molecules into the cell to facilitate its inward diffusion.

Facilitated Diffusion



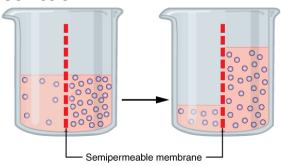


(a) Facilitated diffusion of substances crossing the cell (plasma) membrane takes place with the help of proteins such as channel proteins and carrier proteins. Channel proteins are less selective than carrier proteins, and usually mildly discriminate between their cargo based on size and charge. (b) Carrier proteins are more selective, often only allowing one particular type of molecule to cross.

There are many other solutes that must undergo facilitated diffusion to move into a cell, such as amino acids, or to move out of a cell, such as wastes. Because facilitated diffusion is a passive process, it does not require energy expenditure by the cell.

Water can also move freely across the cell membrane of all cells, either through a protein channel called an aquaporin or by simple diffusion. Waters ability to slip between the lipid tails of the membrane itself via simple diffusion is relatively slow and so most cells rely on aquaporins to increase membrane permeability to water. The number of aquaporins varies across cell types giving different cell types varying degrees of water permeability. When water is transported via these aquaporins from a higher concentration of water to a lower concentration of water this is known as **osmosis** ([link]).

Osmosis

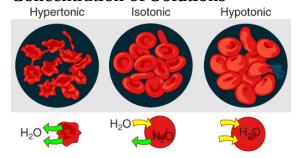


Osmosis is the diffusion of water through a semipermeable membrane down its concentration gradient. If a membrane is permeable to water, though not to a solute, water will equalize its own concentration by diffusing to the side of lower water concentration (and thus the side of higher solute concentration). In the beaker on the left, the solution on the right side of the membrane is hypertonic.

The movement of water molecules is not itself regulated by cells, so it is important that cells are exposed to an environment in which the concentration of solutes outside of the cells (in the extracellular fluid) is equal to the concentration of solutes inside the cells (in the cytoplasm). Two solutions that have the same concentration of solutes are said to be **isotonic** (equal tension). When cells and their extracellular environments are isotonic, the concentration of water molecules is the same outside and inside the cells, and the cells maintain their normal shape (and function).

Osmosis occurs when there is an imbalance of solutes outside of a cell versus inside the cell. A solution that has a higher concentration of solutes than another solution is said to be **hypertonic**, and water molecules tend to diffuse into a hypertonic solution ([link]). Cells in a hypertonic solution will shrivel as water leaves the cell via osmosis. In contrast, a solution that has a lower concentration of solutes than another solution is said to be **hypotonic**, and water molecules tend to diffuse out of a hypotonic solution. Cells in a hypotonic solution will take on too much water and swell, with the risk of eventually bursting. A critical aspect of homeostasis in living things is to create an internal environment in which all of the body's cells are in an isotonic solution. Various organ systems, particularly the kidneys, work to maintain this homeostasis.

Concentration of Solutions



A hypertonic solution has a solute concentration higher than another solution. An isotonic solution has a solute concentration equal to

another solution. A hypotonic solution has a solute concentration lower than another solution.

Another mechanism besides diffusion to passively transport materials between compartments is filtration. Unlike diffusion of a substance from where it is more concentrated to less concentrated, filtration uses a hydrostatic pressure gradient that pushes the fluid—and the solutes within it —from a higher pressure area to a lower pressure area. Filtration is an extremely important process in the body. For example, the circulatory system uses filtration to move plasma and substances across the endothelial lining of capillaries and into surrounding tissues, supplying cells with the nutrients. Filtration pressure in the kidneys provides the mechanism to remove wastes from the bloodstream.

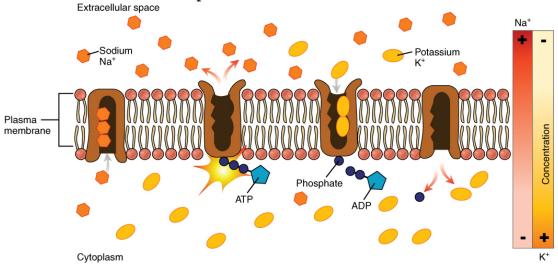
Active Transport

For all of the transport methods described above, the cell expends no energy. Membrane proteins that aid in the passive transport of substances do so without the use of ATP. During active transport, energy is required to move a substance across a membrane, with the help of protein carriers, and usually *against* its concentration gradient.

There are two forms of active transport, primary and secondary. Primary active transport is characterized by the movement of a solute or solutes against the concentration gradient using a carrier protein which is often referred to as a pump. This type of active transport requires direct energy in the form of ATP. Secondary active transport on the other hand, involves the movement of two solutes, one solute along a gradient which releases energy to drive a second solute against it concentration gradient. This type of transport also requires a carrier protein, but the energy used is indirect and is generated by movement of the solute down its gradient. Secondary active transport can be further divided into two forms dependent on the overall

directional movement of solutes: symport (cotransport) and antiport (counter-transport). The most frequently used example of primary active transport is the **sodium-potassium pump**, which is also called Na/K ATPase. These pumps are particularly abundant in nerve cells, which are constantly pumping out sodium ions and pulling in potassium ions to maintain an electrical gradient across their cell membranes ([link]).

Sodium-Potassium Pump



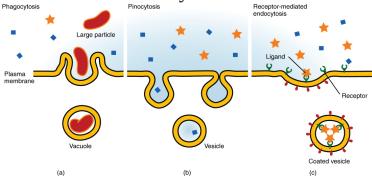
The sodium-potassium pump is found in many cell (plasma) membranes. Powered by ATP, the pump moves sodium and potassium ions in opposite directions, each against its concentration gradient. In a single cycle of the pump, three sodium ions are extruded from and two potassium ions are imported into the cell.

Endocytosis and exocytosis are other forms of active transport but they do not involve membrane carriers. In these forms of bulk transport (also called vesicular transport) energy is needed to accomplish vesicle formation and vesicle movement in the cell. A vesicle is a membranous sac – spherical and hollow organelle bound by a lipid bilayer membrane.

Endocytosis (bringing "into the cell") is the process of a cell ingesting material by enveloping it in a portion of its cell membrane, and then pinching off that portion of membrane ([link]). Once pinched off, the

portion of membrane and its contents becomes an independent, intracellular vesicle. There are three forms of endocytosis: phagocytosis, pinocytosis, and receptor-mediated endocytosis. Phagocytosis ("cell eating") is the endocytosis of large particles. Many immune cells engage in phagocytosis of invading pathogens. Like little Pac-men, their job is to patrol body tissues for unwanted matter, such as invading bacterial cells, phagocytize them, and digest them. When a bacteria for example are phagocytized, the resulting vesicle is called a phagosome. This phagosome then fuses with a lysosome and is now called a phagolysosome. Lysosomes contain digestive enzymes that function in the breaking down the contents in the phagosome. In contrast to phagocytosis, pinocytosis ("cell drinking") brings fluid containing dissolved substances into a cell through membrane vesicles called endosomes.

Three Forms of Endocytosis

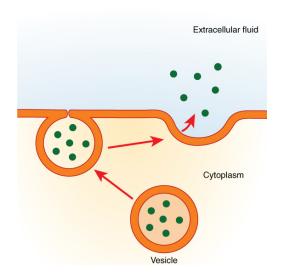


Endocytosis is a form of active transport in which a cell envelopes extracellular materials using its cell membrane. (a) In phagocytosis, which is relatively nonselective, the cell takes in a large particle. (b) In pinocytosis, the cell takes in small particles in fluid. (c) In contrast, receptor-mediated endocytosis is quite selective. When external receptors bind a specific ligand, the cell responds by endocytosing the ligand.

Phagocytosis and pinocytosis take in large portions of extracellular material, and they are typically not highly selective in the substances they bring in. Cells regulate the endocytosis of specific substances via receptormediated endocytosis by taking in specific molecules from the ECF with a minimum of unnecessary fluid. Receptor-mediated endocytosis is endocytosis by a portion of the cell membrane that contains receptors. Once the surface receptors have bound sufficient amounts of the specific substance (the receptor's ligand), the cell will begin to endocytose the part of the membrane containing the receptor-ligand complexes; this invaginated area of the membrane is now called the "coated pit" with membrane proteins called clathrin proteins. When the pit pinches off the resulting vesicle is called a clathrin coated vesicle. It is believed that the clathrin serves as an "address" that directs the vesicle to a certain region of the cell or it may inform other structures in the cell what to do with the vesicle. Iron, a required component of hemoglobin, is endocytosed by red blood cells in this way. Iron is bound to a protein called transferrin in the blood. Specific tranferrin receptors on red blood cell surfaces bind the irontransferrin molecules, and the cell endocytoses the receptor-ligand complexes.

In contrast with endocytosis, **exocytosis** (taking "out of the cell") is the process of a cell exporting material using vesicular transport ([link]). Many cells manufacture substances that must be secreted, like a factory manufacturing a product for export. These substances are typically packaged into membrane-bound vesicles within the cell. When the vesicle membrane fuses with the cell membrane, the vesicle releases its contents into the interstitial fluid. The vesicle membrane then becomes part of the cell membrane. Cells of the stomach and pancreas produce and secrete digestive enzymes through exocytosis ([link]). Endocrine cells produce and secrete hormones that are sent throughout the body, and certain immune cells produce and secrete large amounts of histamine, a chemical important for immune responses.

Exocytosis

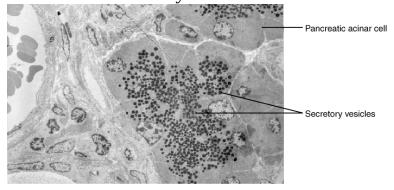


Exocytosis is much like endocytosis in reverse.

Material destined for export is packaged into a vesicle inside the cell.

The membrane of the vesicle fuses with the cell membrane, and the contents are released into the extracellular space.

Pancreatic Cells' Enzyme Products



The pancreatic acinar cells produce and secrete many enzymes that digest food.

The tiny black granules in this electron micrograph are secretory vesicles filled with enzymes that will be exported from the cells via exocytosis. LM × 2900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the University of Michigan WebScope at http://virtualslides.med.umich.edu/Histology/EMsmallCharts/3%20Image%20Scope%20finals/226%20-%20Pancreas 001.svs/view.apml to explore the tissue sample in greater detail.

Note:

Diseases of the...

Cell: Cystic Fibrosis

Cystic fibrosis (CF) affects approximately 30,000 people in the United States, with about 1,000 new cases reported each year. The genetic disease is most well known for its damage to the lungs, causing breathing difficulties and chronic lung infections, but it also affects the liver, pancreas, and intestines. Only about 50 years ago, the prognosis for children born with CF was very grim—a life expectancy rarely over 10

years. Today, with advances in medical treatment, many CF patients live into their 30s.

The symptoms of CF result from a malfunctioning membrane ion channel called the cystic fibrosis transmembrane conductance regulator, or CFTR. In healthy people, the CFTR protein is an integral membrane protein that transports Cl⁻ ions out of the cell. In a person who has CF, the gene for the CFTR is mutated, thus, the cell manufactures a defective channel protein that typically is not incorporated into the membrane, but is instead degraded by the cell.

The CFTR requires ATP in order to function, making its Cl⁻ transport a form of active transport. This characteristic puzzled researchers for a long time because the Cl⁻ ions are actually flowing *down* their concentration gradient when transported out of cells. Active transport generally pumps ions *against* their concentration gradient, but the CFTR presents an exception to this rule.

In normal lung tissue, the movement of Cl⁻ out of the cell maintains a Cl⁻rich, negatively charged environment immediately outside of the cell. This is particularly important in the epithelial lining of the respiratory system. Respiratory epithelial cells secrete mucus, which serves to trap dust, bacteria, and other debris. A cilium (plural = cilia) is one of the hair-like appendages found on certain cells. Cilia on the epithelial cells move the mucus and its trapped particles up the airways away from the lungs and toward the outside. In order to be effectively moved upward, the mucus cannot be too viscous; rather it must have a thin, watery consistency. The transport of Cl⁻ and the maintenance of an electronegative environment outside of the cell attract positive ions such as Na⁺ to the extracellular space. The accumulation of both Cl⁻ and Na⁺ ions in the extracellular space creates solute-rich mucus, which has a low concentration of water molecules. As a result, through osmosis, water moves from cells and extracellular matrix into the mucus, "thinning" it out. This is how, in a normal respiratory system, the mucus is kept sufficiently watered-down to be propelled out of the respiratory system.

If the CFTR channel is absent, Cl⁻ ions are not transported out of the cell in adequate numbers, thus preventing them from drawing positive ions. The absence of ions in the secreted mucus results in the lack of a normal water concentration gradient. Thus, there is no osmotic pressure pulling water into the mucus. The resulting mucus is thick and sticky, and the

ciliated epithelia cannot effectively remove it from the respiratory system. Passageways in the lungs become blocked with mucus, along with the debris it carries. Bacterial infections occur more easily because bacterial cells are not effectively carried away from the lungs.

Chapter Review

Solutes that cross the cell membrane do so using passive (non energy requiring) or active (energy requiring) transport processes. During passive transport, all solutes move by simple diffusion or by facilitated diffusion through the membrane down their concentration gradient. Water diffuses through the membrane in a diffusion process called osmosis. During active transport, energy is expended to assist material movement across the membrane in a direction against their gradient. Active transport may be primary, secondary, or involve bulk transport via vesicles.

Membrane transport is used to maintain homeostasis. At this point, you have been given the nuts and bolts of membrane transport and will be ready to implement that knowledge in the next module, *Digestion and Metabolism*. Please understand that membrane transport does not stop there, we will return to these concepts when we discuss the respiratory and urinary systems.

Glossary

active transport

form of transport across the cell membrane that requires input of cellular energy

amphipathic

describes a molecule that exhibits a difference in polarity between its two ends, resulting in a difference in water solubility

carrier protein

a transmembrane protein that requires binding of a solute that elicits a conformational change to allow solute movement across the cell membrane

cell membrane

membrane surrounding all animal cells, composed of a lipid bilayer interspersed with various molecules; also known as plasma membrane

channel protein

membrane-spanning protein that has an inner pore which allows the passage of one or more substances

concentration gradient

difference in the concentration of a substance between two regions

simple diffusion

movement of a substance from an area of higher concentration to one of lower concentration

electrical gradient

difference in the electrical charge (potential) between two regions

endocytosis

import of material into the cell by formation of a membrane-bound vesicle

exocytosis

export of a substance out of a cell by formation of a membrane-bound vesicle

extracellular fluid (ECF)

fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluid found in other reservoirs in the body

facilitated diffusion

diffusion of a substance with the aid of a membrane protein

glycocalyx

coating of sugar molecules that surrounds the cell membrane

glycoprotein

protein that has one or more carbohydrates attached

hydrophilic

describes a substance or structure attracted to water

hydrophobic

describes a substance or structure repelled by water

hypertonic

describes a solution concentration that is higher than a reference concentration

hypotonic

describes a solution concentration that is lower than a reference concentration

integral protein

membrane-associated protein that spans the entire width of the lipid bilayer

interstitial fluid (IF)

fluid in the small spaces between cells not contained within blood vessels

intracellular fluid (ICF)

fluid in the cytosol of cells

isotonic

describes a solution concentration that is the same as a reference concentration

ligand

molecule that binds with specificity to a specific receptor molecule

osmosis

diffusion of molecules down their concentration across a selectively permeable membrane

passive transport

form of transport across the cell membrane that does not require input of cellular energy

peripheral protein

membrane-associated protein that does not span the width of the lipid bilayer, but is attached peripherally to integral proteins, membrane lipids, or other components of the membrane

phagocytosis

endocytosis of large particles

pinocytosis

endocytosis of fluid

receptor

protein molecule that contains a binding site for another specific molecule (called a ligand)

receptor-mediated endocytosis

endocytosis of ligands attached to membrane-bound receptors

selective permeability

feature of any barrier that allows certain substances to cross but excludes others

sodium-potassium pump

(also, Na⁺/K⁺ ATP-ase) membrane-embedded protein pump that uses ATP to move Na⁺ out of a cell and K⁺ into the cell

vesicle

membrane-bound structure that contains materials within or outside of the cell

OU Human Physiology: Digestion Introduction class="introduction"
Eating Apples

Eating may be one of the simple pleasures in life, but digesting even one apple requires the coordinated work of many organs. (credit: "Aimanness Photography"/Flickr



Note:

Chapter Objectives

After studying this chapter, you will be able to:

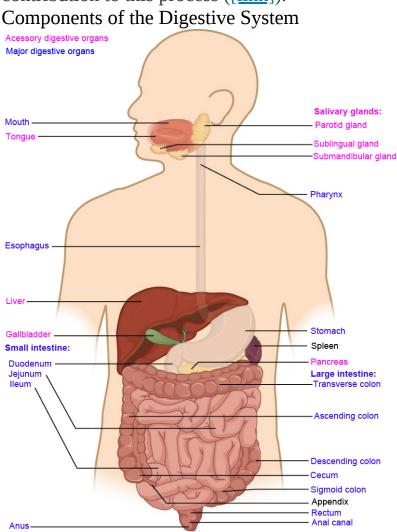
- List and describe the functional anatomy of the organs and accessory organs of the digestive system
- Discuss the processes of ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation
- Discuss the role of the accessory organs in digestion
- Compare and contrast the digestion of the three macronutrients (biomolecules)
- Demonstrate an understanding of membrane transport by relating mechanisms of transport to absorption of nutrients
- Recommend treatments for disorders of the gastrointestinal tract

The digestive system (often called the gastrointestinal system) is continually at work, yet people seldom appreciate the complex tasks it performs in a choreographed biologic symphony. Consider what happens when you eat an apple. Of course, you enjoy the apple's taste as you chew it, but in the hours that follow, unless something goes amiss and you get a stomachache, you don't notice that your digestive system is working. You may be taking a walk or studying or sleeping, having forgotten all about the apple, but your stomach and intestines are busy digesting it and absorbing its vitamins and other nutrients. By the time any waste material is excreted, the body has appropriated all it can use from the apple. In short, whether you pay attention or not, the organs of the digestive system perform their specific functions, allowing you to use the food you eat to keep you going. This chapter examines the structure and functions of these organs, and explores the mechanics and chemistry of the digestive processes.

OU Human Physiology: Overview of the Digestive System By the end of this section, you will be able to:

- Identify the major organs of the alimentary canal from proximal to distal, and briefly state their function
- Identify the accessory digestive organs and briefly state their function
- Describe the four fundamental tissue layers of the alimentary canal

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process ([link]).



All digestive organs play integral roles in the life-sustaining process of digestion.

As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. [link] gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

Contribution of Other Body Systems to the Digestive System	
Body system Benefits received by the digestive system	
Cardiovascular	Blood supplies digestive organs with oxygen and processed nutrients

Contribution of Other Body Systems to the Digestive System		
Body system	Benefits received by the digestive system	
Endocrine	Endocrine hormones help regulate secretion in digestive glands and accessory organs	
Integumentary	Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption	
Lymphatic	Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream	
Muscular	Skeletal muscles support and protect abdominal organs	
Nervous	Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract	
Respiratory	Respiratory organs provide oxygen and remove carbon dioxide	
Skeletal	Bones help protect and support digestive organs	
Urinary	Kidneys convert vitamin D into its active form, allowing calcium absorption in the small intestine	

Digestive System Organs

The easiest way to understand the digestive system is to divide its organs into two main categories. The first group is the organs that make up the alimentary canal. These organs are often called the major structures of the gastrointestinal tract because they form the passageway through which food

and digestive products are conducted. Accessory digestive organs comprise the second group and are critical for orchestrating the breakdown of food and the assimilation of its nutrients into the body. Accessory digestive organs, despite their name, are critical to the function of the digestive system.

Alimentary Canal Organs

Also called the gastrointestinal (GI) tract or gut, the **alimentary canal** (aliment- = "to nourish") is a one-way tube about 7.62 meters (25 feet) in length during life and closer to 10.67 meters (35 feet) in length when measured after death, once smooth muscle tone is lost. The main function of the organs of the alimentary canal is to nourish the body. This tube begins at the mouth and terminates at the anus. Between those two points, the canal is modified as the pharynx, esophagus, stomach, and small and large intestines to fit the functional needs of the body ([link]). Both the mouth and anus are open to the external environment; thus, food and wastes within the alimentary canal are technically considered to be outside the body. Only through the process of absorption do the nutrients in food enter into and nourish the body's "inner space."

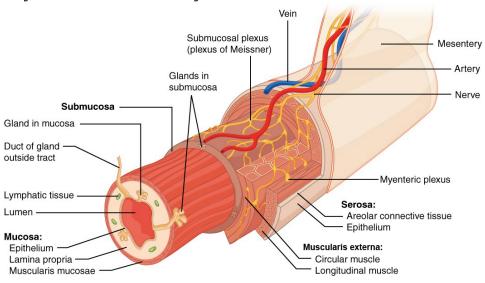
Accessory Structures

Each accessory digestive organ aids in the breakdown of food ([link]). Within the mouth, the teeth and tongue begin mechanical digestion, whereas the salivary glands begin chemical digestion. Once food products enter the small intestine, the gallbladder, liver, and pancreas release secretions—such as bile and enzymes—essential for digestion to continue. Together, these are called accessory organs because they sprout from the lining cells of the developing gut (mucosa) and augment its function; indeed, you could not live without their vital contributions, and many significant diseases result from their malfunction. Even after development is complete, they maintain a connection to the gut by way of ducts.

Histology of the Alimentary Canal

Throughout its length, the alimentary tract is composed of the same four tissue layers; the details of their structural arrangements vary to fit their specific functions. Starting from the lumen and moving outwards, these layers are the mucosa, submucosa, muscularis externa, and serosa, which is continuous with the mesentery (see [link]).

Layers of the Alimentary Canal



The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis externa, and serosa.

The **mucosa** is referred to as a mucous membrane, because mucus production is a characteristic feature of gut epithelium. The membrane consists of epithelium, which is in direct contact with ingested food, and the lamina propria, a layer of connective tissue analogous to the dermis. In addition, the mucosa has a thin, smooth muscle layer, called the muscularis mucosa (not to be confused with the muscularis layer, described below).

Epithelium—The epithelium is in direct contact with the lumen, the space inside the alimentary canal. Interspersed among its epithelial cells are goblet cells, which secrete mucus and fluid into the lumen, and

enteroendocrine cells, which secrete hormones into the interstitial spaces between cells. Epithelial cells have a very brief lifespan, averaging from only a couple of days (in the mouth) to about a week (in the gut). This process of rapid renewal helps preserve the health of the alimentary canal, despite the wear and tear resulting from continued contact with foodstuffs.

Lamina propria—In addition to loose connective tissue, the lamina propria contains numerous blood and lymphatic vessels that transport nutrients absorbed through the alimentary canal to other parts of the body. The lamina propria also serves an immune function by housing clusters of lymphocytes, making up the mucosa-associated lymphoid tissue (MALT). These lymphocyte clusters are particularly substantial in the distal ileum where they are known as Peyer's patches. When you consider that the alimentary canal is exposed to foodborne bacteria and other foreign matter, it is not hard to appreciate why the immune system has evolved a means of defending against the pathogens encountered within it.

Muscularis mucosa—This thin layer of smooth muscle is in a constant state of tension, pulling the mucosa of the stomach and small intestine into undulating folds. These folds dramatically increase the surface area available for digestion and absorption.

As its name implies, the **submucosa** lies immediately beneath the mucosa. A broad layer of dense connective tissue, it connects the overlying mucosa to the underlying muscularis and allows the gastrointestinal tract to stretch without damaging it. It includes blood and lymphatic vessels (which transport absorbed nutrients), and a scattering of submucosal glands that release digestive secretions. Additionally, it serves as a conduit for a dense branching network of enteric nerves, the submucosal plexus, which functions as described below.

The third layer of the alimentary canal is the **muscalaris externa**. The muscularis externa in the small intestine is made up of a double layer of smooth muscle: an inner circular layer and an outer longitudinal layer. The contractions of these layers promote mechanical digestion, expose more of the food to digestive chemicals, and move the food along the canal. In the most proximal and distal regions of the alimentary canal, including the mouth, pharynx, anterior part of the esophagus, and external anal sphincter,

the muscularis externa is made up of skeletal muscle, which gives you voluntary control over swallowing and defecation. The basic two-layer structure found in the small intestine is modified in the organs proximal and distal to it. The stomach is equipped for its churning function by the addition of a third layer, the oblique muscle. While the colon has two layers like the small intestine, its longitudinal layer is segregated into three narrow parallel bands, the taenia coli, which make it look like a series of pouches rather than a simple tube. This layer also consists of enteric nerve branches called the myenteric plexus.

The **serosa** is the portion of the alimentary canal superficial to the muscularis externa. Present only in the region of the alimentary canal within the abdominal cavity, it consists of a layer of visceral peritoneum overlying a layer of loose connective tissue. Instead of serosa, the mouth, pharynx, and esophagus have a dense sheath of collagen fibers called the adventitia. These tissues serve to hold the alimentary canal in place near the ventral surface of the vertebral column.

Nerve Supply

As food enters the mouth, it is detected by receptors that send impulses along the sensory neurons of cranial nerves. Without these nerves, not only would your food be without taste, but you would also be unable to feel either the food or the structures of your mouth, and you would be unable to avoid biting yourself as you chew, an action enabled by the motor branches of cranial nerves.

Intrinsic innervation of much of the alimentary canal is provided by the enteric nervous system, which runs from the esophagus to the anus, and contains approximately 100 million motor, sensory, and interneurons (unique to this system compared to all other parts of the peripheral nervous system). These enteric neurons are grouped into two plexuses. The **myenteric plexus** (plexus of Auerbach) lies in the muscularis layer of the alimentary canal and is responsible for **motility**, especially the rhythm and force of the contractions of the muscularis. The **submucosal plexus** (plexus of Meissner) lies in the submucosal layer and is responsible for regulating digestive secretions and reacting to the presence of food (see [link]).

Extrinsic innervations of the alimentary canal are provided by the autonomic nervous system, which includes both sympathetic and parasympathetic nerves. In general, sympathetic activation (the fight-or-flight response) restricts the activity of enteric neurons, thereby decreasing GI secretion and motility. In contrast, parasympathetic activation (the rest-and-digest response) increases GI secretion and motility by stimulating neurons of the enteric nervous system.

Blood Supply

The blood vessels serving the digestive system have two functions. They transport the protein and carbohydrate nutrients absorbed by mucosal cells after food is digested in the lumen. Lipids are absorbed via lacteals, tiny structures of the lymphatic system. The blood vessels' second function is to supply the organs of the alimentary canal with the nutrients and oxygen needed to drive their cellular processes.

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.

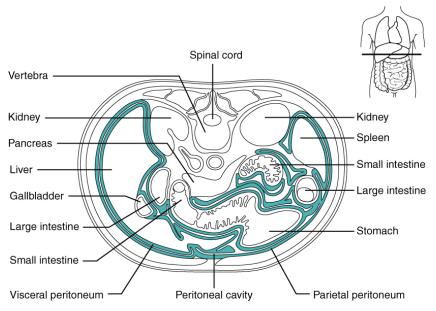
The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are "resting and digesting," about one-fourth of the blood pumped with each heartbeat enters arteries serving the intestines.

The Peritoneum

The digestive organs within the abdominal cavity are held in place by the peritoneum, a broad serous membranous sac made up of squamous

epithelial tissue surrounded by connective tissue. It is composed of two different regions: the parietal peritoneum, which lines the abdominal wall, and the visceral peritoneum, which envelopes the abdominal organs ([link]). The peritoneal cavity is the space bounded by the visceral and parietal peritoneal surfaces. A few milliliters of watery fluid act as a lubricant to minimize friction between the serosal surfaces of the peritoneum.

The Peritoneum



A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum (darker lines).

Note:

Disorders of the...

Digestive System: Peritonitis

Inflammation of the peritoneum is called peritonitis. Chemical peritonitis can develop any time the wall of the alimentary canal is breached, allowing the contents of the lumen entry into the peritoneal cavity. For example, when an ulcer perforates the stomach wall, gastric juices spill into the peritoneal cavity. Hemorrhagic peritonitis occurs after a ruptured tubal

pregnancy or traumatic injury to the liver or spleen fills the peritoneal cavity with blood. Even more severe peritonitis is associated with bacterial infections seen with appendicitis, colonic diverticulitis, and pelvic inflammatory disease (infection of uterine tubes, usually by sexually transmitted bacteria). Peritonitis is life threatening and often results in emergency surgery to correct the underlying problem and intensive antibiotic therapy. When your great grandparents and even your parents were young, the mortality from peritonitis was high. Aggressive surgery, improvements in anesthesia safety, the advance of critical care expertise, and antibiotics have greatly improved the mortality rate from this condition. Even so, the mortality rate still ranges from 30 to 40 percent.

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as **retroperitoneal**.

Note:



By clicking on this <u>link</u> you can watch a short video of what happens to the food you eat, as it passes from your mouth to your intestine. Along the

way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

Chapter Review

The digestive system includes the organs of the alimentary canal and accessory structures. The alimentary canal forms a continuous tube that is open to the outside environment at both ends. The organs of the alimentary canal are the mouth, pharynx, esophagus, stomach, small intestine, and large intestine. The accessory digestive structures include the teeth, tongue, salivary glands, liver, pancreas, and gallbladder. The wall of the alimentary canal is composed of four basic tissue layers: mucosa, submucosa, muscularis externa, and serosa. The enteric nervous system provides intrinsic innervation, and the autonomic nervous system provides extrinsic innervation.

Glossary

accessory digestive organ

includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas

alimentary canal

continuous muscular digestive tube that extends from the mouth to the anus

motility

movement of food through the GI tract

mucosa

innermost lining of the alimentary canal

muscularis externa

muscle (skeletal or smooth) layer of the alimentary canal wall

myenteric plexus

(plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility

retroperitoneal

located posterior to the peritoneum

serosa

outermost layer of the alimentary canal wall present in regions within the abdominal cavity

submucosa

layer of dense connective tissue in the alimentary canal wall that binds the overlying mucosa to the underlying muscularis

submucosal plexus

(plexus of Meissner) nerve supply that regulates activity of glands and smooth muscle

OU Human Physiology: Digestive System Processes By the end of this section, you will be able to:

• Discuss six fundamental activities of the digestive system, giving an example of each

The digestive system uses mechanical and chemical activities to break food down into absorbable substances during its journey through the digestive system. [link] provides an overview of the basic functions of the digestive organs.

Note:



Visit this <u>site</u> for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.

Functions of the Digestive Organs		
Organ	Major functions	Other functions

Functions of the Digestive Organs		
Organ	Major functions	Other functions
Mouth	Ingests food Chews and mixes food Begins chemical breakdown of carbohydrates Moves food into the pharynx Begins breakdown of lipids via lingual lipase	Moistens and dissolves food, allowing you to taste it Cleans and lubricates the teeth and oral cavity Has some antimicrobial activity
Pharynx	Propels food from the oral cavity to the esophagus	Lubricates food and passageways
Esophagus	Propels food to the stomach	Lubricates food and passageways

Functions of the Digestive Organs			
Organ	Major functions	Other functions	
Stomach	Mixes and churns food with gastric juices to form chyme Begins chemical breakdown of proteins Releases food into the duodenum as chyme Absorbs some fatsoluble substances (for example, alcohol, aspirin) Possesses antimicrobial functions	Stimulates proteindigesting enzymes Secretes intrinsic factor required for vitamin B ₁₂ absorption in small intestine	

Functions of the Digestive Organs		
Organ	Major functions	Other functions
Small intestine	Mixes chyme with digestive juices Propels food at a rate slow enough for digestion and absorption Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water Performs physical digestion via segmentation	Provides optimal medium for enzymatic activity

Functions of the Digestive Organs			
Organ	Major functions	Other functions	
Accessory	Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption Gallbladder: stores, concentrates, and releases bile Pancreas: produces digestive enzymes and bicarbonate	Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity	
Large intestine	Further breaks down food residues Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria Propels feces toward rectum Eliminates feces	Food residue is concentrated and temporarily stored prior to defecation Mucus eases passage of feces through colon	

Digestive Processes

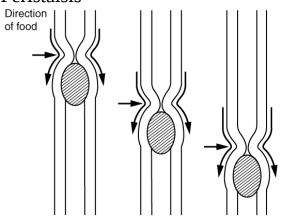
The processes of digestion includes: ingestion, propulsion, mechanical or physical digestion, chemical digestion via secretion, absorption, and

defecation.

The first of these processes, **ingestion**, refers to the entry of food into the alimentary canal through the mouth. There, the food is chewed and mixed with saliva, which contains enzymes that begin breaking down the carbohydrates in the food plus some lipid digestion via lingual lipase. Chewing increases the surface area of the food and allows an appropriately sized bolus to be produced.

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of **propulsion**, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. **Peristalsis** consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along ([link]). These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.

Peristalsis



Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation. Digestion includes both mechanical and chemical processes. Mechanical **digestion** is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes **mastication**, or chewing, as well as tongue movements that help break food into smaller bits and mix food with saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic "soup" called **chyme**. **Segmentation**, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

In **chemical digestion**, starting in the mouth, digestive secretions break down complex food molecules into their chemical building blocks (for example, proteins into separate amino acids). These secretions vary in composition, but typically contain water, various enzymes, acids, and salts. The process is completed in the small intestine.

Food that has been broken down is of no value to the body unless it enters the bloodstream and its nutrients are put to work. This occurs through the process of **absorption**, which takes place primarily within the small intestine. There, most nutrients are absorbed from the lumen of the alimentary canal into the bloodstream through the epithelial cells that make up the mucosa. Lipids are absorbed into lacteals and are transported via the lymphatic vessels to the bloodstream. The details of these processes will be discussed later.

In **defecation**, the final step in digestion, undigested materials are removed from the body as feces.

Note:

Aging and the...

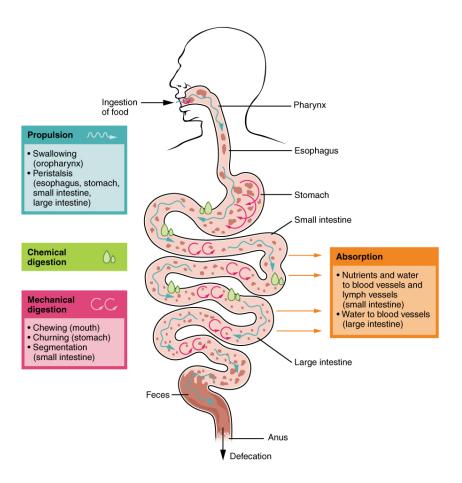
Digestive System: From Appetite Suppression to Constipation

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn't as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren't producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal ([link]).

Digestive Processes



The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.

Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

Chapter Review

The digestive system ingests and digests food, absorbs released nutrients, and excretes food components that are indigestible. The activities involved in this process are ingestion, motility, mechanical digestion, chemical digestion, absorption, and defecation. These processes are regulated by neural and hormonal mechanisms that will be discussed later.

Glossary

absorption

passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals

chemical digestion

enzymatic breakdown of food

chyme

soupy liquid created when food is mixed with digestive juices

defecation

elimination of undigested substances from the body in the form of feces

ingestion

taking food into the GI tract through the mouth

mastication

chewing

mechanical digestion

chewing, mixing, and segmentation that prepares food for chemical digestion

peristalsis

muscular contractions and relaxations that propel food through the GI tract

propulsion

voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

segmentation

alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it apart and mixing it with digestive juices OU Human Physiology: The Mouth, Pharynx, and Esophagus By the end of this section, you will be able to:

- Describe the structures of the mouth, including its three accessory digestive organs
- Trace the pathway food follows from ingestion into the mouth through release into the stomach

In this section, you will examine the anatomy and functions of the three main organs of the upper alimentary canal—the mouth, pharynx, and esophagus—as well as three associated accessory organs—the tongue, salivary glands, and teeth.

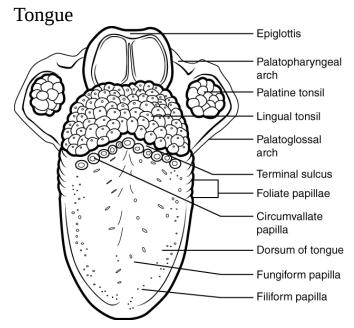
The Tongue

Perhaps you have heard it said that the **tongue** is the strongest muscle in the body. Those who stake this claim cite its strength proportionate to its size. Although it is difficult to quantify the relative strength of different muscles, it remains indisputable that the tongue is a workhorse, facilitating ingestion, mechanical digestion, chemical digestion (lingual lipase), sensation (of taste, texture, and temperature of food), swallowing, and vocalization.

Extrinsic muscles of the tongue originate outside the tongue and insert into connective tissues within the tongue. Working in concert, these muscles perform three important digestive functions in the mouth: (1) position food for optimal chewing, (2) gather food into a **bolus** (rounded mass), and (3) position food so it can be swallowed.

The top and sides of the tongue are studded with papillae, extensions of lamina propria of the mucosa ([link]). The exact names of these papillae are not important for our purposes; however understanding the function of papilla is important to understanding digestion. Some papilla contain taste buds while other have touch receptors that help the tongue move the food around in the mouth and some create an abrasive surface that performs mechanically, much like a cat's rough tongue that is used for grooming. Lingual glands in the lamina propria of the tongue secrete mucus and a watery serous fluid that contains the enzyme **lingual lipase**, which plays a

minor role in breaking down triglycerides but does not begin working until it is activated in the stomach.



This superior view of the tongue shows the locations and types of lingual papillae.

The Salivary Glands

Many small **salivary glands** are housed within the mucous membranes of the mouth and tongue. These minor exocrine glands are constantly secreting saliva, either directly into the oral cavity or indirectly through ducts, even while you sleep. In fact, an average of 1 to 1.5 liters of saliva is secreted each day. Usually just enough saliva is present to moisten the mouth and teeth. Secretion increases when you eat, because saliva is essential to moisten food and initiate the chemical breakdown of carbohydrates. Small amounts of saliva are also secreted by the labial glands in the lips. In addition, the buccal glands in the cheeks, palatal glands in the palate, and lingual glands in the tongue help ensure that all areas of the mouth are supplied with adequate saliva.

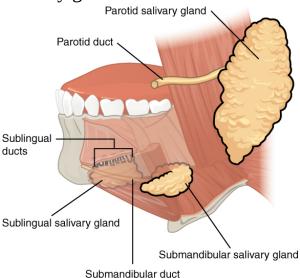
The Major Salivary Glands

Outside the oral mucosa are three pairs of major salivary glands the submandibular, sublingual, and parotid glands. These glands secrete the majority of saliva into ducts that open into the mouth ([link]).

Saliva

Saliva is essentially (95.5 percent) water. The remaining 4.5 percent is a complex mixture of ions, glycoproteins, enzymes, growth factors, and waste products. Perhaps the most important ingredient in salvia from the perspective of digestion is the enzyme salivary amylase, which initiates the breakdown of carbohydrates. Food does not spend enough time in the mouth to allow all the carbohydrates to break down, but salivary amylase continues acting until it is inactivated by stomach acids. Bicarbonate and phosphate ions function as chemical buffers, maintaining saliva at a pH between 6.35 and 6.85. Salivary mucus helps lubricate food, facilitating movement in the mouth, bolus formation, and swallowing. Saliva contains immunoglobulin A, which prevents microbes from penetrating the epithelium, and lysozyme, which makes saliva antimicrobial. Saliva also contains epidermal growth factor, which might have given rise to the adage "a mother's kiss can heal a wound."

Salivary glands



The major salivary glands are located outside the oral mucosa and deliver saliva into the mouth through ducts.

Note:

Homeostatic Imbalances

The Parotid Glands: Mumps

Infections of the nasal passages and pharynx can attack any salivary gland. The parotid glands are the usual site of infection with the virus that causes mumps (paramyxovirus). Mumps manifests by enlargement and inflammation of the parotid glands, causing a characteristic swelling between the ears and the jaw. Symptoms include fever and throat pain, which can be severe when swallowing acidic substances such as orange juice.

In about one-third of men who are past puberty, mumps also causes testicular inflammation, typically affecting only one testis and rarely resulting in sterility. With the increasing use and effectiveness of mumps vaccines, the incidence of mumps has decreased dramatically. According to the U.S. Centers for Disease Control and Prevention (CDC), the number of mumps cases dropped from more than 150,000 in 1968 to fewer than 1700 in 1993 to only 11 reported cases in 2011.

The Teeth

The teeth, or **dentes** (singular = dens), are organs similar to bones that you use to tear, grind, and otherwise mechanically break down food. During the course of your lifetime, you have two sets of teeth (one set of teeth is a **dentition**. Your 20 **deciduous teeth**, or baby teeth, first begin to appear at about 6 months of age. Between approximately age 6 and 12, these teeth are replaced by 32 **permanent teeth**.

Digestive Functions of the Mouth		
Structure	Action	Outcome
Lips and cheeks	Confine food between teeth	Food is chewed evenly during mastication
Salivary glands	Secrete saliva	Moisten and lubricate the lining of the mouth and pharynx Moisten, soften, and dissolve food Clean the mouth and teeth Salivary amylase breaks down starch
Tongue's extrinsic muscles	Move tongue sideways, and in and out	Manipulate food for chewing Shape food into a bolus Manipulate food for swallowing
Tongue's intrinsic muscles	Change tongue shape	Manipulate food for swallowing
Taste buds	Sense food in mouth and sense taste	Nerve impulses from taste buds are conducted to salivary nuclei in the brain stem and then to salivary glands, stimulating saliva secretion

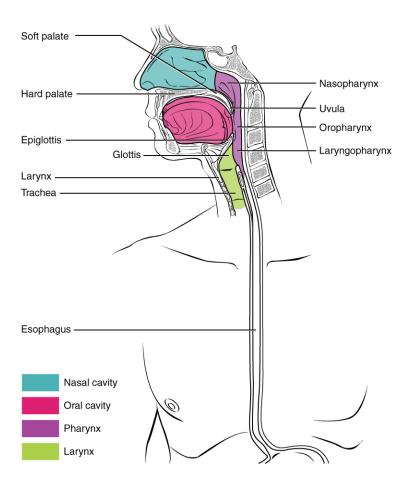
Digestive Functions of the Mouth		
Structure	Action Outcome	
Lingual glands	Secrete lingual lipase	Activated in the stomach Break down triglycerides into fatty acids and diglycerides
Teeth	Shred and crush food	Break down solid food into smaller particles for swallowing

The Pharynx

The **pharynx** (throat) is involved in both digestion and respiration. It receives food and air from the mouth, and air from the nasal cavities. When food enters the pharynx, involuntary muscle contractions close off the air passageways ([link]).

A short tube of skeletal muscle lined with a mucous membrane, the pharynx runs from the throat to the opening of the esophagus and larynx. Air enters the larynx and trachea via the glottis and goes to the lungs while food enters the esophagus which runs parallel to the trachea. When the food "goes down the wrong way," it goes into the trachea. When food enters the trachea, the reaction is to cough, which usually forces the food up and out of the trachea, and back into the pharynx.

Pharynx



The pharynx runs from the nostrils to the esophagus and the larynx.

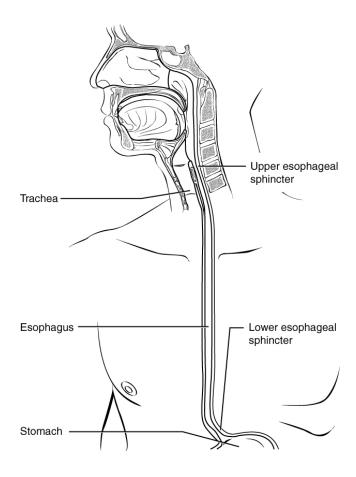
The Esophagus

The **esophagus** is a muscular tube that connects the pharynx to the stomach. It is approximately 25.4 cm (10 in) in length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus ([link]).

Passage of Food through the Esophagus

The **upper esophageal sphincter**, which is continuous with the inferior pharyngeal constrictor, controls the movement of food from the pharynx into the esophagus. The upper two-thirds of the esophagus consists of both smooth and skeletal muscle fibers, with the latter fading out in the bottom third of the esophagus. Rhythmic waves of peristalsis, which begin in the upper esophagus, propel the bolus of food toward the stomach. Meanwhile, secretions from the esophageal mucosa lubricate the esophagus and food. Food passes from the esophagus into the stomach at the **lower esophageal sphincter** (also called the gastroesophageal or cardiac sphincter). Recall that sphincters are muscles that surround tubes and serve as valves, closing the tube when the sphincters contract and opening it when they relax. The lower esophageal sphincter relaxes to let food pass into the stomach, and then contracts to prevent stomach acids from backing up into the esophagus. Surrounding this sphincter is the muscular diaphragm, which helps close off the sphincter when no food is being swallowed. When the lower esophageal sphincter does not completely close, the stomach's contents can reflux (that is, back up into the esophagus), causing heartburn or gastroesophageal reflux disease (GERD).

Esophagus



The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach.

Histology of the Esophagus

The mucosa of the esophagus is made up of an epithelial lining that protects against erosion from food particles. The mucosa's lamina propria contains mucus-secreting glands. The muscularis layer changes according to location: In the upper third of the esophagus, the muscularis is skeletal

muscle. In the middle third, it is both skeletal and smooth muscle. In the lower third, it is smooth muscle. As mentioned previously, the most superficial layer of the esophagus is called the adventitia, not the serosa. In contrast to the stomach and intestines, the loose connective tissue of the adventitia is not covered by a fold of visceral peritoneum. The digestive functions of the esophagus are identified in [link].

Digestive Functions of the Esophagus	
Action	Outcome
Upper esophageal sphincter relaxation	Allows the bolus to move from the laryngopharynx to the esophagus
Peristalsis	Propels the bolus through the esophagus
Lower esophageal sphincter relaxation	Allows the bolus to move from the esophagus into the stomach and prevents chyme from entering the esophagus
Mucus secretion	Lubricates the esophagus, allowing easy passage of the bolus

Chapter Review

In the mouth, the tongue and the teeth begin mechanical digestion, and saliva begins chemical digestion. The pharynx, which plays roles in breathing and vocalization as well as digestion, runs from the nasal and oral

cavities superiorly to the esophagus inferiorly (for digestion) and to the larynx anteriorly (for respiration). During deglutition (swallowing), the soft palate rises to close off the nasopharynx, the larynx elevates, and the epiglottis folds over the glottis. The esophagus includes an upper esophageal sphincter made of skeletal muscle, which regulates the movement of food from the pharynx to the esophagus. It also has a lower esophageal sphincter, made of smooth muscle, which controls the passage of food from the esophagus to the stomach. Cells in the esophageal wall secrete mucus that eases the passage of the food bolus.

Glossary

bolus

mass of chewed food

deciduous tooth one of 20 "baby teeth"

deglutition

three-stage process of swallowing

dens

tooth

dentition

set of teeth

esophagus

muscular tube that runs from the pharynx to the stomach

lingual lipase

digestive enzyme from glands in the tongue that acts on triglycerides

lower esophageal sphincter

smooth muscle sphincter that regulates food movement from the esophagus to the stomach

permanent tooth

one of 32 adult teeth

pharynx

throat

saliva

aqueous solution of proteins and ions secreted into the mouth by the salivary glands

salivary amylase

digestive enzyme in saliva that acts on starch

salivary gland

an exocrine gland that secretes a digestive fluid called saliva

tongue

accessory digestive organ of the mouth, the bulk of which is composed of skeletal muscle

upper esophageal sphincter

skeletal muscle sphincter that regulates food movement from the pharynx to the esophagus

OU Human Physiology: The Stomach By the end of this section, you will be able to:

- Identify the three major anatomical regions of the stomach, and its sphincter
- Identify the four main types of secreting cells in gastric glands, and their important products
- Explain why the stomach does not digest itself
- Describe the mechanical and chemical digestion of food entering the stomach
- Recommend treatments for gastric disorders

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person's stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food —such as at holiday dinner—you stretch the stomach more than when you eat less.

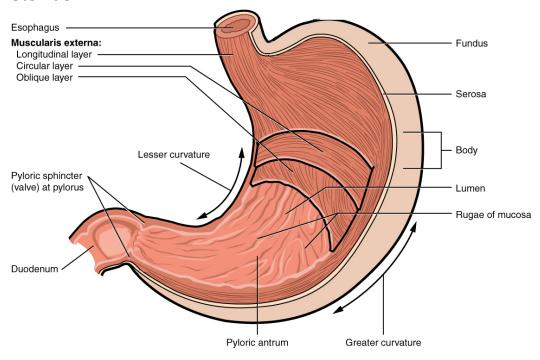
Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

Structure

There are three anatomical regions in the **stomach**: fundus, body, and antrum—sometimes called the pyloric antrum ([link]). Located inferior to the diaphragm is the dome-shaped **fundus**. Below the fundus is the **body**, the main part of the stomach and a lower region called the antrum. The pylorus is also important, however not one of the three <u>major</u> anatomical region as it connects the stomach to the duodenum. The smooth muscle **pyloric sphincter** is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a **ruga**.

Stomach

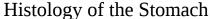


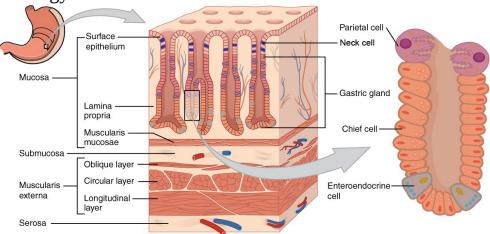
The stomach has three major anatomical regions: fundus, body, and antrum. The addition of an inner oblique smooth

muscle layer gives the muscularis the ability to vigorously churn and mix food.

Histology

The wall of the stomach is made of the same four layers as most of the rest of the alimentary canal, but with adaptations to the mucosa and muscularis for the unique functions of this organ. In addition to the typical circular and longitudinal smooth muscle layers, the muscularis has an inner oblique smooth muscle layer ([link]). As a result, in addition to moving food through the canal, the stomach can vigorously churn food, mechanically breaking it down into smaller particles.





The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin.

The stomach mucosa's epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. A vast number of **gastric**

pits dot the surface of the epithelium, giving it the appearance of a well-used pincushion, and mark the entry to each **gastric gland**, which secretes a complex digestive fluid referred to as gastric juice.

Although the walls of the gastric pits are made up primarily of mucus cells, the gastric glands are made up of different types of cells. The glands of the fundus and pylorus are composed primarily of mucus-secreting cells. Cells that make up the pyloric antrum secrete mucus and a number of hormones, including the majority of the stimulatory hormone, **gastrin**. The much larger glands of the fundus and body of the stomach, the site of most chemical digestion, produce most of the gastric secretions. These glands are made up of a variety of secretory cells. These include parietal cells, chief cells, mucous neck cells, and enteroendocrine cells.

Parietal cells—Located in the gastric glands are **parietal cells**, which are among the most highly differentiated of the body's epithelial cells. These relatively large cells produce both **hydrochloric acid (HCl)** and **intrinsic factor**. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B_{12} in the small intestine.

Chief cells—Located in the gastric glands are **chief cells**, which secrete **pepsinogen**, the inactive proenzyme (precursor) form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.

Mucous neck cells—Gastric glands in the upper part of the stomach contain **mucous neck cells** that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.

Enteroendocrine cells—Finally, **enteroendocrine cells** found in the gastric glands secrete various hormones into the interstitial fluid of the lamina propria. These include gastrin, which is released mainly by enteroendocrine **G cells**.

Note:



Watch this <u>animation</u> that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

The Mucosal Barrier

The mucosa of the stomach is exposed to the highly corrosive acidity of gastric juice. Gastric enzymes that can digest protein can also digest the stomach itself. The stomach is protected from self-digestion by the **mucosal barrier**. This barrier has several components. First, the stomach wall is covered by a thick coating of bicarbonate-rich mucus. This mucus forms a physical barrier, and its bicarbonate ions neutralize acid. Second, the epithelial cells of the stomach's mucosa meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers. Finally, stem cells located where gastric glands join the gastric pits quickly replace damaged epithelial mucosal cells, when the epithelial cells are shed. In fact, the surface epithelium of the stomach is completely replaced every 3 to 6 days.

Note:

Homeostatic Imbalances

Ulcers: When the Mucosal Barrier Breaks Down

As effective as the mucosal barrier is, it is not a "fail-safe" mechanism. Sometimes, gastric juice eats away at the superficial lining of the stomach

mucosa, creating erosions, which mostly heal on their own. Deeper and larger erosions are called ulcers.

Why does the mucosal barrier break down? A number of factors can interfere with its ability to protect the stomach lining. The majority of all ulcers are caused by either excessive intake of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, or *Helicobacter pylori* infection.

Antacids help relieve symptoms of ulcers such as "burning" pain and indigestion. When ulcers are caused by NSAID use, switching to other classes of pain relievers allows healing. When caused by *H. pylori* infection, antibiotics are effective.

A potential complication of ulcers is perforation: Perforated ulcers create a hole in the stomach wall, resulting in peritonitis (inflammation of the peritoneum). These ulcers must be repaired surgically.

Digestive Functions of the Stomach

The stomach participates in virtually all the digestive activities with the exception of ingestion and defecation. Although almost all absorption takes place in the small intestine, the stomach does absorb some nonpolar substances, such as alcohol and aspirin.

Mechanical Digestion

Within a few moments after food after enters your stomach, mixing waves begin to occur at intervals of approximately 20 seconds. A **mixing wave** is a unique type of peristalsis that mixes and softens the food with gastric juices to create chyme. The initial mixing waves are relatively gentle, but these are followed by more intense waves, starting at the body of the stomach and increasing in force as they reach the pylorus. It is fair to say that long before your sushi exits through the pyloric sphincter, it bears little resemblance to the sushi you ate.

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called **gastric emptying**, rhythmic mixing waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin. During infancy, gastric glands also produce rennin, an enzyme that helps digest milk protein.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B_{12} , which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach

removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B₁₂ injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

Chapter Review

The stomach participates in all digestive activities except ingestion and defecation. It vigorously churns food. It secretes gastric juices that break down food and absorbs certain drugs, including aspirin and some alcohol. The stomach begins the digestion of protein and continues the digestion of carbohydrates and fats. It stores food as an acidic liquid called chyme, and releases it gradually into the small intestine through the pyloric sphincter.

Glossary

body

mid-portion of the stomach

chief cell

gastric gland cell that secretes pepsinogen

enteroendocrine cell

gastric gland cell that releases hormones

fundus

dome-shaped region of the stomach above and to the left of the cardia

G cell

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gastrin-secreting enteroendocrine cell
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gastric emptying

process by which mixing waves gradually cause the release of chyme into the duodenum

gastric gland

gland in the stomach mucosal epithelium that produces gastric juice

gastric pit

narrow channel formed by the epithelial lining of the stomach mucosa

gastrin

peptide hormone that stimulates secretion of hydrochloric acid and gut motility

hydrochloric acid (HCl)

digestive acid secreted by parietal cells in the stomach

intrinsic factor

glycoprotein required for vitamin B₁₂ absorption in the small intestine

mixing wave

unique type of peristalsis that occurs in the stomach

mucosal barrier

protective barrier that prevents gastric juice from destroying the stomach itself

mucous neck cell

gastric gland cell that secretes a uniquely acidic mucus

parietal cell

gastric gland cell that secretes hydrochloric acid and intrinsic factor

pepsinogen

inactive form of pepsin

pyloric sphincter

sphincter that controls stomach emptying

ruga

fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

stomach

alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine

OU Human Physiology: The Small and Large Intestines By the end of this section, you will be able to:

- Compare and contrast the location and gross anatomy of the small and large intestines
- Identify three main adaptations of the small intestine wall that increase its absorptive capacity
- Describe the mechanical and chemical digestion of chyme upon its release into the small intestine
- List three features unique to the wall of the large intestine and identify their contributions to its function
- Identify the beneficial roles of the bacterial flora in digestive system functioning
- Trace the pathway of food waste from its point of entry into the large intestine through its exit from the body as feces

The word intestine is derived from a Latin root meaning "internal," and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the "guts," they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

The Small Intestine

Chyme released from the stomach enters the **small intestine**, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called "small." In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we'll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m², more than 100 times the surface area of your skin. This large

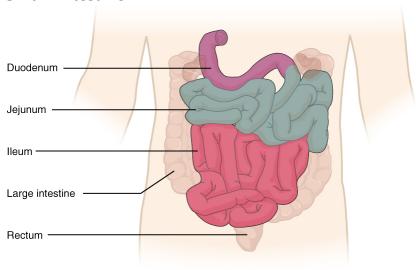
surface area is necessary for complex processes of digestion and absorption that occur within it.

Structure

The coiled tube of the small intestine is subdivided into three regions. From proximal (at the stomach) to distal, these are the duodenum, jejunum, and ileum ([link]).

The shortest region is the 25.4-cm (10-in) **duodenum**, which begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum.

Small Intestine

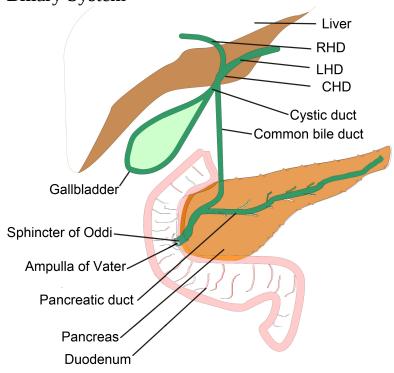


The three regions of the small intestine are the duodenum, jejunum, and ileum.

Of particular interest is the **ampulla of Vater** (hepatopancreatic ampulla). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the

bile duct (through which bile passes from the liver) and the **main pancreatic duct** (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum. The **sphincter of Oddi** (hepatopancreatic sphincter) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum ([link]).

Biliary System



RHD: Rt hepatic duct, LHD: Lt. hepatic duct, CHD: Comm. hepatic duct

Bile is produced in the liver and stored in the gallbladder. The bile is then transported through a series of ducts to the duodenum. The bile is emptied into the duodenum via the ampulla of Vater when the sphincter of Oddi is relaxed. (credit: Drriad)

The **jejunum** is about 0.9 meters (3 feet) long (in life) and runs from the duodenum to the ileum. Jejunum means "empty" in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at

death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

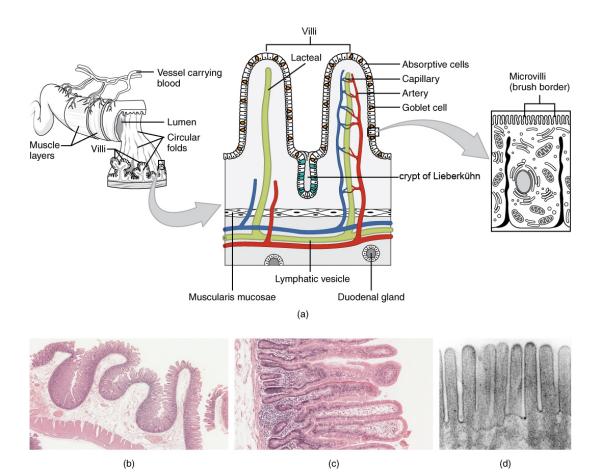
The **ileum** is the longest part of the small intestine, measuring about 1.8 meters (6 feet) in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the **ileocecal sphincter** (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

Parasympathetic nerve fibers from the vagus nerve and sympathetic nerve fibers from the thoracic splanchnic nerve provide extrinsic innervation to the small intestine. The superior mesenteric artery is its main arterial supply. Veins run parallel to the arteries and drain into the superior mesenteric vein. Nutrient-rich blood from the small intestine is then carried to the liver via the hepatic portal vein.

Histology

The wall of the small intestine is composed of the same four layers typically present in the alimentary system. However, three features of the mucosa and submucosa are unique. These features, which increase the absorptive surface area of the small intestine more than 600-fold, include circular folds, villi, and microvilli ([link]). These adaptations are most abundant in the proximal two-thirds of the small intestine, where the majority of absorption occurs.

Histology of the Small Intestine



(a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli.
(b) Micrograph of the circular folds. (c) Micrograph of the villi.
(d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (credit b-d: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Circular folds

Also called a plica circulare, a **circular fold** is a deep ridge in the mucosa and submucosa. Beginning near the proximal part of the duodenum and

ending near the middle of the ileum, these folds facilitate absorption. Their shape causes the chyme to spiral, rather than move in a straight line, through the small intestine. Spiraling slows the movement of chyme and provides the time needed for nutrients to be fully absorbed.

Villi

Within the circular folds are small (0.5–1 mm long) hairlike vascularized projections called **villi** (singular = villus) that give the mucosa a furry texture. There are about 20 to 40 villi per square millimeter, increasing the surface area of the epithelium tremendously. The mucosal epithelium, primarily composed of absorptive cells, covers the villi. Absorptive cells aid in digestion and absorption of nutrients in chyme. Goblet cells on the other hand secrete mucus into the lumen of the small intestine. In addition to muscle and connective tissue to support its structure, each villus contains a capillary bed composed of one arteriole and one venule, as well as a lymphatic capillary called a **lacteal**. The breakdown products of carbohydrates and proteins (sugars and amino acids) can enter the bloodstream directly, but lipid breakdown products are absorbed by the lacteals and transported to the bloodstream via the lymphatic system.

Microvilli

As their name suggests, **microvilli** (singular = microvillus) are much smaller (1 μ m) than villi. They are cylindrical apical surface extensions of the plasma membrane of the mucosa's epithelial cells, and are supported by microfilaments within those cells. Although their small size makes it difficult to see each microvillus, their combined microscopic appearance suggests a mass of bristles, which is termed the **brush border**. Fixed to the surface of the microvilli membranes are enzymes that finish digesting carbohydrates and proteins. There are an estimated 200 million microvilli per square millimeter of small intestine, greatly expanding the surface area of the plasma membrane and thus greatly enhancing absorption.

Intestinal Glands

In addition to the three specialized absorptive features just discussed, the mucosa between the villi is dotted with deep crevices that each lead into a tubular **crypt of Lieberkühn** (intestinal gland), which is formed by cells that line the crevices (see [link]). These produce **intestinal juice**, a slightly alkaline (pH 7.4 to 7.8) mixture of water and mucus. Each day, about 0.95 to 1.9 liters (1 to 2 quarts) are secreted in response to the distention of the small intestine or the irritating effects of chyme on the intestinal mucosa.

The submucosa of the duodenum is the only site of the complex mucussecreting **duodenal glands** (Brunner's glands), which produce a bicarbonate-rich alkaline mucus that buffers the acidic chyme as it enters from the stomach.

Intestinal MALT

The lamina propria of the small intestine mucosa is studded with quite a bit of MALT. In addition to solitary lymphatic nodules, aggregations of intestinal MALT, which are typically referred to as Peyer's patches, are concentrated in the distal ileum, and serve to keep bacteria from entering the bloodstream. Peyer's patches are most prominent in young people and become less distinct as you age, which coincides with the general activity of our immune system.

Note:



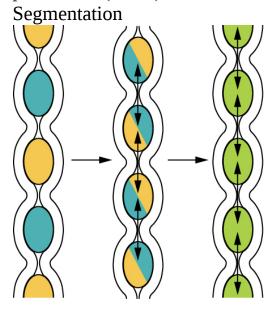
Watch this <u>animation</u> that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption

of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

Mechanical Digestion in the Small Intestine

The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute ([link]).



Segmentation separates chyme and then pushes it

back together, mixing it and providing time for digestion and absorption.

When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone **motilin**, which initiates peristalsis in the form of a **migrating motility complex**. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First, digestive activity in the stomach provokes the **gastroileal reflex**, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes about 3 to 5 hours for all chyme to leave the small intestine.

Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Although some proteins arriving in the small intestine

may already be broken into smaller peptides, other proteins have yet to be broken down. Enzymatic degradation of proteins in the small intestine is dependent on a brush border enzyme, enterokinase, which activates zymogens (protease precursors) coming from the pancreas. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine's absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal surfaces of the mucosal cells.

For optimal chemical digestion, chyme must be delivered from the stomach slowly and in small amounts. This is because chyme from the stomach is typically hypertonic, and if large quantities were forced all at once into the small intestine, the resulting osmotic water loss from the blood into the intestinal lumen would result in potentially life-threatening low blood volume. In addition, continued digestion requires an upward adjustment of the low pH of stomach chyme, along with rigorous mixing of the chyme with bile and pancreatic juices. Both processes take time, so the pumping action of the pylorus must be carefully controlled to prevent the duodenum from being overwhelmed with chyme.

Note:

Disorders of the...

Small Intestine: Lactose Intolerance

Lactose intolerance is a condition characterized by indigestion caused by dairy products. It occurs when the absorptive cells of the small intestine do not produce enough lactase, the enzyme that digests the milk sugar lactose. In most mammals, lactose intolerance increases with age. In contrast, some human populations, most notably Caucasians, are able to maintain the ability to produce lactase as adults.

In people with lactose intolerance, the lactose in chyme is not digested. Bacteria in the large intestine ferment the undigested lactose, a process that produces gas. In addition to gas, symptoms include abdominal cramps, bloating, and diarrhea. Symptom severity ranges from mild discomfort to severe pain; however, symptoms resolve once the lactose is eliminated in feces.

The hydrogen breath test is used to help diagnose lactose intolerance. Lactose-tolerant people have very little hydrogen in their breath. Those with lactose intolerance exhale hydrogen, which is one of the gases produced by the bacterial fermentation of lactose in the colon. After the hydrogen is absorbed from the intestine, it is transported through blood vessels into the lungs. There are a number of lactose-free dairy products available in grocery stores. In addition, dietary supplements are available. Taken with food, they provide lactase to help digest lactose.

The Large Intestine

The **large intestine** is the terminal part of the alimentary canal. The primary function of this organ is to finish absorption of nutrients and water, synthesize certain vitamins, form feces, and eliminate feces from the body.

Structure

The large intestine runs from the appendix to the anus. It frames the small intestine on three sides. Despite its being about one-half as long as the small intestine, it is called large because it is more than twice the diameter of the small intestine, about 3 inches.

Subdivisions

The large intestine is subdivided into four main regions: the cecum, the colon, the rectum, and the anus. The ileocecal valve, located at the opening

between the ileum and the large intestine, controls the flow of chyme from the small intestine to the large intestine.

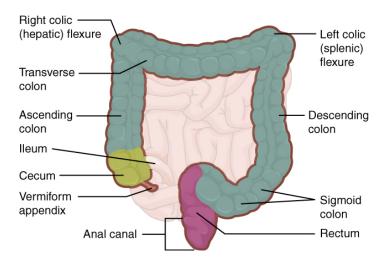
Cecum

The first part of the large intestine is the **cecum**, a sac-like structure that is suspended inferior to the ileocecal valve. It is about 6 cm (2.4 in) long, receives the contents of the ileum, and continues the absorption of water and salts. The **appendix** (or vermiform appendix) is a winding tube that attaches to the cecum. Although the 7.6-cm (3-in) long appendix contains lymphoid tissue, suggesting an immunologic function, this organ is generally considered vestigial. However, at least one recent report postulates a survival advantage conferred by the appendix: In diarrheal illness, the appendix may serve as a bacterial reservoir to repopulate the enteric bacteria for those surviving the initial phases of the illness. Moreover, its twisted anatomy provides a haven for the accumulation and multiplication of enteric bacteria.

Colon

The cecum blends seamlessly with the **colon**. Upon entering the colon, the food residue first travels up the **ascending colon** on the right side of the abdomen. At the inferior surface of the liver, the colon bends and becomes the **transverse colon**. The region defined as hindgut begins with the last third of the transverse colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen. From there, food residue passes through the **descending colon**, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped **sigmoid colon**, which extends medially to the midline ([link]). The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

Large Intestine



The large intestine includes the cecum, colon, and rectum.

Note:

Homeostatic Imbalances

Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.

Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

Rectum

Food residue leaving the sigmoid colon enters the **rectum** in the pelvis. Even though rectum is Latin for "straight," this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the **rectal valves**. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

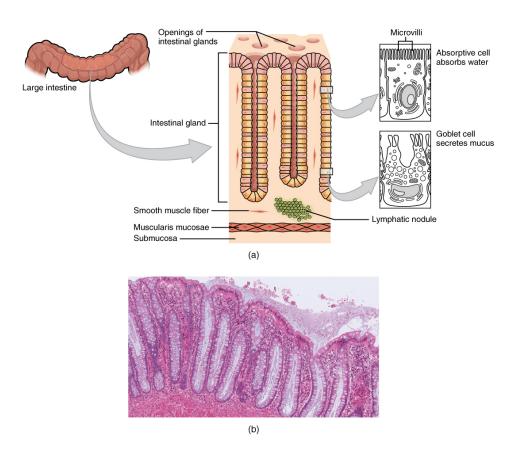
Anal Canal

Finally, food residue reaches the last part of the large intestine, the **anal canal**, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in) long structure opens to the exterior of the body at the anus. The anal canal includes two sphincters. The **internal anal sphincter** is made of smooth muscle, and its contractions are involuntary. The **external anal sphincter** is made of skeletal muscle, which is under voluntary control. Except when defecating, both usually remain closed.

Histology

There are several notable differences between the walls of the large and small intestines ([link]). For example, few enzyme-secreting cells are found in the wall of the large intestine, and there are no circular folds or villi. Other than in the anal canal, the mucosa of the colon is simple columnar epithelium made mostly of enterocytes (absorptive cells) and goblet cells. In addition, the wall of the large intestine has far more crypts of Lieberkühn, which contain a vast population of enterocytes and goblet cells. These goblet cells secrete mucus that eases the movement of feces and protects the intestine from the effects of the acids and gases produced by enteric bacteria. The enterocytes absorb water and salts as well as vitamins produced by your intestinal bacteria.

Histology of the Large Intestine



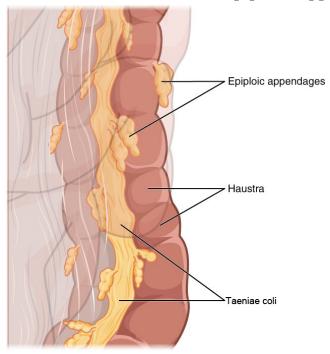
(a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon's simple columnar epithelium and goblet cells. LM x 464. (credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages ([link]). The **teniae coli** are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called **haustra**

(singular = hostrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled sacs of visceral peritoneum called **epiploic appendages**. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.

Taeniae Coli, Haustra, and Epiploic Appendages



Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the **bacterial flora**. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier.

Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a colectomy. Often, a new fecal pouch can be crafted from the small intestine and sutured to the anus, but if not, an ileostomy can be created by bringing the distal ileum through the abdominal wall, allowing the watery chyme to be collected in a bag-like adhesive appliance.

Mechanical Digestion

In the large intestine, mechanical digestion begins when chyme moves from the ileum into the cecum, an activity regulated by the ileocecal sphincter. Right after you eat, peristalsis in the ileum forces chyme into the cecum. When the cecum is distended with chyme, contractions of the ileocecal sphincter strengthen. Once chyme enters the cecum, colon movements begin.

Mechanical digestion in the large intestine includes a combination of three types of movements. The presence of food residues in the colon stimulates a slow-moving **haustral contraction**. This type of movement involves sluggish segmentation, primarily in the transverse and descending colons. When a haustrum is distended with chyme, its muscle contracts, pushing the residue into the next haustrum. These contractions occur about every 30 minutes, and each last about 1 minute. These movements also mix the food residue, which helps the large intestine absorb water. The second type of movement is peristalsis, which, in the large intestine, is slower than in the more proximal portions of the alimentary canal. The third type is a **mass movement**. These strong waves start midway through the transverse colon and quickly force the contents toward the rectum. Mass movements usually occur three or four times per day, either while you eat or immediately afterward. Distension in the stomach and the breakdown products of

digestion in the small intestine provoke the **gastrocolic reflex**, which increases motility, including mass movements, in the colon. Fiber in the diet both softens the stool and increases the power of colonic contractions, optimizing the activities of the colon.

Chemical Digestion

Although the glands of the large intestine secrete mucus, they do not secrete digestive enzymes. Therefore, chemical digestion in the large intestine occurs exclusively because of bacteria in the lumen of the colon. Through the process of **saccharolytic fermentation**, bacteria break down some of the remaining carbohydrates. This results in the discharge of hydrogen, carbon dioxide, and methane gases that create **flatus** (gas) in the colon; flatulence is excessive flatus. Each day, up to 1500 mL of flatus is produced in the colon. More is produced when you eat foods such as beans, which are rich in otherwise indigestible sugars and complex carbohydrates like soluble dietary fiber.

Absorption, Feces Formation, and Defecation

The small intestine absorbs about 90 percent of the water you ingest (either as liquid or within solid food). The large intestine absorbs most of the remaining water, a process that converts the liquid chyme residue into semisolid **feces** ("stool"). Feces is composed of undigested food residues, unabsorbed digested substances, millions of bacteria, old epithelial cells from the GI mucosa, inorganic salts, and enough water to let it pass smoothly out of the body. Of every 500 mL (17 ounces) of food residue that enters the cecum each day, about 150 mL (5 ounces) become feces.

Feces are eliminated through contractions of the rectal muscles. You help this process by a voluntary procedure called **Valsalva's maneuver**, in which you increase intra-abdominal pressure by contracting your diaphragm and abdominal wall muscles, and closing your glottis.

The process of defecation begins when mass movements force feces from the colon into the rectum, stretching the rectal wall and provoking the defecation reflex, which eliminates feces from the rectum. This parasympathetic reflex is mediated by the spinal cord. It contracts the sigmoid colon and rectum, relaxes the internal anal sphincter, and initially contracts the external anal sphincter. The presence of feces in the anal canal sends a signal to the brain, which gives you the choice of voluntarily opening the external anal sphincter (defecating) or keeping it temporarily closed. If you decide to delay defecation, it takes a few seconds for the reflex contractions to stop and the rectal walls to relax. The next mass movement will trigger additional defecation reflexes until you defecate.

If defecation is delayed for an extended time, additional water is absorbed, making the feces firmer and potentially leading to constipation. On the other hand, if the waste matter moves too quickly through the intestines, not enough water is absorbed, and diarrhea can result. This can be caused by the ingestion of foodborne pathogens. In general, diet, health, and stress determine the frequency of bowel movements. The number of bowel movements varies greatly between individuals, ranging from two or three per day to three or four per week.

Note:



By watching this <u>animation</u> you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

Chapter Review

The three main regions of the small intestine are the duodenum, the jejunum, and the ileum. The small intestine is where digestion is completed and virtually all absorption occurs. These two activities are facilitated by structural adaptations that increase the mucosal surface area by 600-fold, including circular folds, villi, and microvilli. There are around 200 million microvilli per square millimeter of small intestine, which contain brush border enzymes that complete the digestion of carbohydrates and proteins. Combined with pancreatic juice, intestinal juice provides the liquid medium needed to further digest and absorb substances from chyme. The small intestine is also the site of unique mechanical digestive movements. Segmentation moves the chyme back and forth, increasing mixing and opportunities for absorption. Migrating motility complexes propel the residual chyme toward the large intestine.

The main regions of the large intestine are the cecum, the colon, and the rectum. The large intestine absorbs water and forms feces, and is responsible for defecation. Bacterial flora break down additional carbohydrate residue, and synthesize certain vitamins. The mucosa of the large intestinal wall is generously endowed with goblet cells, which secrete mucus that eases the passage of feces. The entry of feces into the rectum activates the defecation reflex.

Glossary

ampulla of Vater

(also, hepatopancreatic ampulla) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite

anal canal

final segment of the large intestine

appendix

(vermiform appendix) coiled tube attached to the cecum

ascending colon

first region of the colon

bacterial flora

bacteria in the large intestine

brush border

fuzzy appearance of the small intestinal mucosa created by microvilli

cecum

pouch forming the beginning of the large intestine

circular fold

(also, plica circulare) deep fold in the mucosa and submucosa of the small intestine

colon

part of the large intestine between the cecum and the rectum

crypt of Lieberkühn

(also, intestinal gland) gland in the small intestinal mucosa that secretes intestinal juice

descending colon

part of the colon between the transverse colon and the sigmoid colon

duodenal gland

(also, Brunner's gland) mucous-secreting gland in the duodenal submucosa

duodenum

first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum

epiploic appendage

small sac of fat-filled visceral peritoneum attached to teniae coli

external anal sphincter

voluntary skeletal muscle sphincter in the anal canal

feces

semisolid waste product of digestion

flatus

gas in the intestine

gastrocolic reflex

propulsive movement in the colon activated by the presence of food in the stomach

gastroileal reflex

long reflex that increases the strength of segmentation in the ileum

haustrum

small pouch in the colon created by tonic contractions of teniae coli

haustral contraction

slow segmentation in the large intestine

ileocecal sphincter

sphincter located where the small intestine joins with the large intestine

ileum

end of the small intestine between the jejunum and the large intestine

internal anal sphincter

involuntary smooth muscle sphincter in the anal canal

intestinal juice

mixture of water and mucus that helps absorb nutrients from chyme

jejunum

middle part of the small intestine between the duodenum and the ileum

lacteal

lymphatic capillary in the villi

large intestine

terminal portion of the alimentary canal

main pancreatic duct

(also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas

mass movement

long, slow, peristaltic wave in the large intestine

microvillus

small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

migrating motility complex

form of peristalsis in the small intestine

motilin

hormone that initiates migrating motility complexes

rectal valve

one of three transverse folds in the rectum where feces is separated from flatus

rectum

part of the large intestine between the sigmoid colon and anal canal

saccharolytic fermentation

anaerobic decomposition of carbohydrates

sigmoid colon

end portion of the colon, which terminates at the rectum

small intestine

section of the alimentary canal where most digestion and absorption occurs

sphincter of Oddi

(also, hepatopancreatic sphincter) sphincter regulating the flow of bile and pancreatic juice into the duodenum

teenia coli

one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the terminal end

transverse colon

part of the colon between the ascending colon and the descending colon

Valsalva's maneuver

voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation

villus

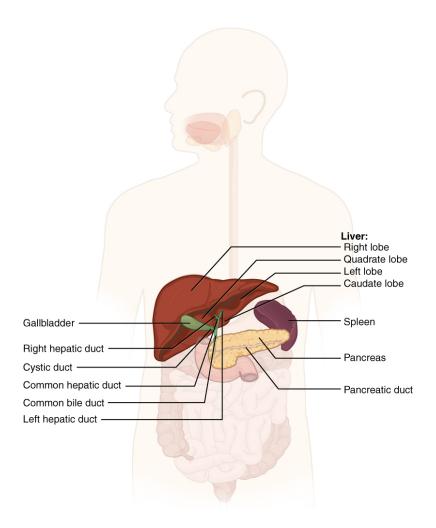
projection of the mucosa of the small intestine

OU Human Physiology: Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder
By the end of this section, you will be able to:

- State the digestive roles of the liver, pancreas, and gallbladder
- Discuss the composition and function of bile
- Identify the enzymes and buffers present in pancreatic juice
- Describe the function of the enzymes and buffers in pancreatic juice
- Discuss how proteolytic enzymes (zyomogens) are produced in the pancreas
- Discuss the activation of zymogens by the duodenum
- Describe the pathway for bile and pancreatic juice to arrive in duodenum
- Illustrate the importance of enzyme pH to function

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder ([link]). The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.

Accessory Organs



The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.

The Liver

The **liver** is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles in metabolism and regulation. The liver lies inferior to the diaphragm in the abdominal cavity and receives protection from the surrounding ribs.

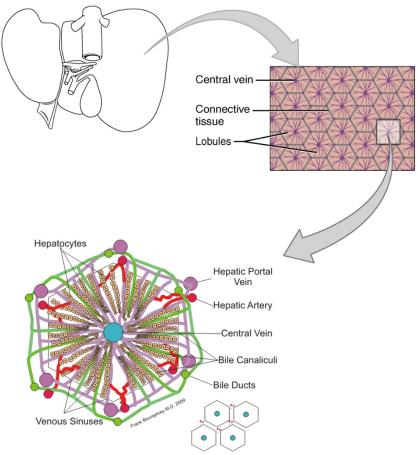
There are two major blood vessels that penetrate the liver. The **hepatic artery** delivers oxygenated blood from the heart to the liver. The **hepatic portal vein** delivers partially deoxygenated blood containing nutrients absorbed from the small intestine to the liver. In addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the central vein and then through the hepatic vein to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.

Histology

The liver has three main components: hepatocytes, bile canaliculi, and hepatic sinusoids([link]). A hepatocyte is the liver's main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory, metabolic, and endocrine functions. Plates of hepatocytes called hepatic laminae radiate outward from the portal vein in each hepatic lobule.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each **bile canaliculus** (plural = canaliculi). These small ducts accumulate the bile produced by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the **common hepatic duct**. This duct then joins with the cystic duct from the gallbladder, forming the **common bile duct** through which bile flows into the small intestine.

Microscopic Anatomy of the Liver



Basic Structure of Liver Lobule

The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein. (Credit for the basic Liver Lobule Dr. Frank Boumphrey)

A **hepatic sinusoid** is an open, porous blood space formed by fenestrated capillaries from nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries. Hepatocytes are tightly packed around the fenestrated endothelium of these spaces, giving them easy access to the blood. From their central position, hepatocytes process the nutrients, toxins, and waste materials carried by the blood. Materials such as bilirubin are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids or just stored in

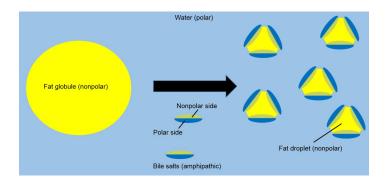
the cells until called upon. The hepatic sinusoids combine and send blood to a **central vein**. Blood then flows through a **hepatic vein** into the inferior vena cava. This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-shaped **reticuloendothelial cells** (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The **portal triad** is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid globules, a process called emulsification. **Bile** is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μ m in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity([link]). This is the same way dish soap works on fats mixed with water.

Emulsification of a Fat Globule

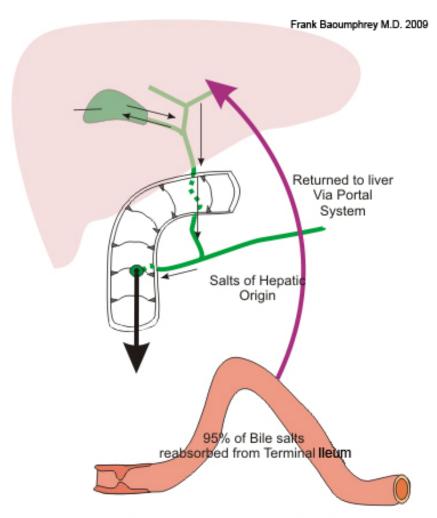


Since bile salts are amphipathic, containing both polar and nonpolar parts, they are able to interact with both water and fat molecules. This interaction allows the bile salts to emulsify large fat globules into smaller fat droplets which increases surface area to let lipases to breakdown fats.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the **enterohepatic circulation** ([link]). Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like ampulla of Vater closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.

Enterohepatic Circulation



Enterohepatic circulation of Bile salts

Bile salts end up in the ileum and are recycled back into the liver via the portal system. (Credit for figure: Dr. Frank Boumphrey)

In addition to the liver's function as an accessory digestive organ, the liver is also important in metabolism and regulation. We will be discussing each of these functions in further detail at a later time. Additional functions of the liver include:

1. Removal of old red blood cells from the blood. **Bilirubin**, the main bile pigment, is a waste product produced when macrophages in the spleen removes old or damaged red blood cells from the circulation.

These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats are broken down or absorbed. We will return to this concept at a later time.

- 2. Metabolic processing of the major categories of nutrients **after** a meal. Following a meal, the liver will convert some of the absorbed glucose into a stored form of sugar called glycogen (a process called glycogenesis) and some absorbed amino acids will be converted to fatty acids. The liver will also synthesize triglycerides and cholesterol and use them to synthesize lipoproteins which are then secreted into the bloodstream.
- 3. Metabolic processing of the major categories of nutrients **between** meals. During periods in which nutrients are not being absorbed, the liver will breakdown glycogen into glucose (a process called glycogenolysis) and produce glucoses from a process called gluconeogenesis. The liver will also convert fatty acids to ketones and synthesizes urea from ammonia, which is a product of protein catabolism.
- 4. Synthesis and modification of hormones. The liver synthesizes hormones such as thrombopoietin which stimulates platelet production, and insulin-like growth factor. The liver also metabolizes hormones and eliminates them from the body.
- 5. Synthesis of plasma proteins. The liver synthesizes proteins needed for blood clotting, those that transport steroid, thyroid hormones, and cholesterol in the blood, and angiotensinogen which plays a role in the renin-angiotensin system.
- 6. Elimination of wastes from the body. Breakdown products of hemoglobin from destruction of red blood cells are eliminated by the body in the feces. Excess cholesterol, insulin, drugs and toxins are also eliminated from the body via the liver either via the feces or

- chemically transforming them so that they can be dissolved in the plasma and eliminated by the kidneys.
- 7. Storage of essential molecules. The liver can store glycogen, as well as vitamins (such as A, D, and B12) and metals (such as iron and copper).

Note:



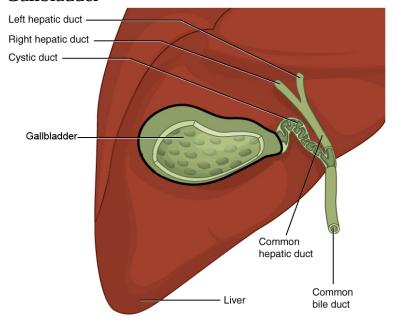
Watch this <u>video</u> to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

The Gallbladder

The **gallbladder** is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the **cystic duct** and into the common bile duct and into the duodenum via the Ampulla of Vater when the sphincter of Oddi is relaxed([link]). The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.

Gallbladder

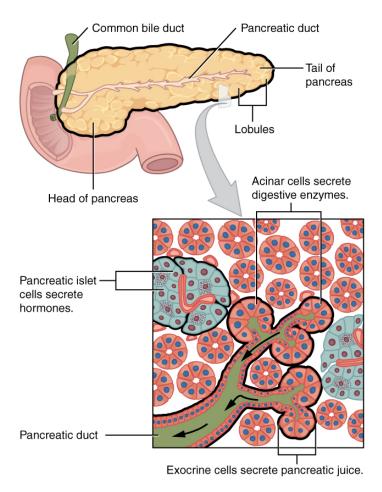


The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.

The Pancreas

The soft, oblong, glandular **pancreas** lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the "c-shaped" curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions ([link]).

Exocrine and Endocrine Pancreas



The pancreas has a head, a body, and a

tail. It delivers pancreatic juice to the duodenum through the pancreatic duct.

The exocrine part of the pancreas arises as little grape-like cell clusters, each called an **acinus** (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich **pancreatic juice** into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver and gallbladder) just before entering the duodenum via a common opening (the Ampulla of Vater). The smooth muscle sphincter of the Ampulla of Vater controls the release of pancreatic juice and bile into the small intestine.

Scattered through the sea of exocrine acini are small islands of endocrine cells, the islets of Langerhans. These vital cells produce the hormones pancreatic polypeptide, insulin, glucagon, and somatostatin.

Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms called zymogens. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme **enteropeptidase** stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Chapter Review

Chemical digestion in the small intestine cannot occur without the help of the liver and pancreas. The liver produces bile and delivers it to the common hepatic duct. Bile contains bile salts and phospholipids, which emulsify large lipid globules into tiny lipid droplets, a necessary step in lipid digestion and absorption. The gallbladder stores and concentrates bile, releasing it when it is needed by the small intestine. The pancreas produces the enzyme- and bicarbonate-rich pancreatic juice and delivers it to the small intestine through ducts. Pancreatic juice buffers the acidic gastric juice in chyme, inactivates pepsin from the stomach, and enables the optimal functioning of digestive enzymes in the small intestine.

Glossary

acinus

cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas

bile

alkaline solution produced by the liver and important for the emulsification of lipids

bile canaliculus

small duct between hepatocytes that collects bile

bilirubin

main bile pigment, which is responsible for the brown color of feces

central vein

vein that receives blood from hepatic sinusoids

common bile duct

structure formed by the union of the common hepatic duct and the gallbladder's cystic duct

common hepatic duct

duct formed by the merger of the two hepatic ducts

cystic duct

duct through which bile drains and enters the gallbladder

enterohepatic circulation

recycling mechanism that conserves bile salts

enterokinase

(also, enteropeptidase) intestinal brush-border enzyme that activates trypsinogen to trypsin

gallbladder

accessory digestive organ that stores and concentrates bile

hepatic artery

artery that supplies oxygenated blood to the liver

hepatic lobule

hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein

hepatic portal vein

vein that supplies deoxygenated nutrient-rich blood to the liver

hepatic sinusoid

blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery

hepatic vein

vein that drains into the inferior vena cava

hepatocytes

major functional cells of the liver

liver

largest gland in the body whose main digestive function is the production of bile

pancreas

accessory digestive organ that secretes pancreatic juice

pancreatic juice

secretion of the pancreas containing digestive enzymes and bicarbonate

portal triad

bile duct, hepatic artery branch, and hepatic portal vein branch

reticuloendothelial cell

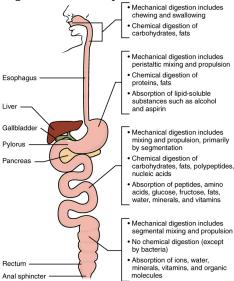
(also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

OU Human Physiology: Chemical Digestion and Absorption: A Closer Look By the end of this section, you will be able to:

- Identify the locations and secretions involved in the chemical digestion of carbohydrates, proteins, lipids, and nucleic acids
- List enzymes important in digestion of carbohydrates, proteins, lipids, and nucleic acids
- · Compare and contrast absorption of the nutrients in each organ of the gastrointestinal tract
- Describe the importance of the secretions involved in digestion
- Demonstrate an understanding of membrane transport by relating mechanisms to absorption of nutrients
- Recommend treatments for malabsorption of nutrients

As you have learned, the process of mechanical digestion is relatively simple. It involves the physical breakdown of food but does not alter its chemical makeup. Chemical digestion, on the other hand, is a complex process that reduces food into its chemical building blocks, which are then absorbed to nourish the cells of the body ([link]). In this section, you will look more closely at the processes of chemical digestion and absorption.

Digestion and Absorption



Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine.

Chemical Digestion

Large food molecules (for example, proteins, lipids, nucleic acids, and starches) must be broken down into subunits that are small enough to be absorbed by the lining of the alimentary canal. This is accomplished by enzymes through hydrolysis. The many enzymes involved in chemical digestion are summarized in [link].

The Digestive Enzymes

EheyDig estiv Category	ve Enzymes Enzyme Name	Source	Substrate	Product	
	Enzyme Name	Source	Substrate	Product	
Enzyme Category	Enzyme Name	Source	Substrate	Product	
Salivary Enzymes	Lingual lipase	Lingual glands	Triglycerides	Free fatty acids, and mono- and diglyceride	
Salivary Enzymes	Salivary amylase	Salivary glands	Polysaccharides	Disaccharides and trisaccharides such as maltose and limit dextrins	
Gastric enzymes	Gastric lipase	Chief cells	Triglycerides	Fatty acids and monoacylglycerides	
Gastric enzymes	Pepsin*	Chief cells	Proteins	Peptides	
Brush border enzymes	α-Dextrinase	Small intestine	α-Dextrins	Glucose	
Brush border enzymes	Enteropeptidase	Small intestine	Trypsinogen	Trypsin	
Brush border enzymes	Lactase	Small intestine	Lactose	Glucose and galactose	
Brush border enzymes	Maltase	Small intestine	Maltose	Glucose	
Brush border enzymes	Nucleosidases and phosphatases	Small intestine	Nucleotides	Phosphates, nitrogenous bases, and pentoses	
Brush border enzymes	Peptidases	Small intestine	Aminopeptidase: amino acids at the amino end of peptides Dipeptidase: dipeptides	Aminopeptidase: amino acids and peptides Dipeptidase: amino acids	
Brush border enzymes	Sucrase	Small intestine	Sucrose	Glucose and fructose	

The Digestive Enzymes

Enzyme Category	Enzyme Name	Source	Substrate	Product
Pancreatic enzymes	Carboxy- peptidase*	Pancreatic acinar cells	Amino acids at the carboxyl end of peptides	Amino acids and peptides
Pancreatic enzymes	Chymotrypsin*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Elastase*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Nucleases	Pancreatic acinar cells	Ribonuclease: ribonucleic acids Deoxyribonuclease: deoxyribonucleic acids	Nucleotides
Pancreatic enzymes	Pancreatic amylase	Pancreatic acinar cells	Polysaccharides (starches)	α-Dextrins, disaccharides (maltose), trisaccharides (maltotriose)
Pancreatic enzymes	Pancreatic lipase	Pancreatic acinar cells	Triglycerides that have been emulsified by bile salts	Fatty acids and monoacylglycerides
Pancreatic enzymes	Trypsin*	Pancreatic acinar cells	Proteins	Peptides

^{*}These enzymes have been activated by other substances.

Carbohydrate Digestion

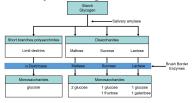
The average American diet is about 50 percent carbohydrates, which may be classified according to the number of monomers they contain of simple sugars (monosaccharides and disaccharides) and/or complex sugars (polysaccharides). Glucose, galactose, and fructose are the three monosaccharides that are commonly consumed and are readily absorbed. Your digestive system is also able to break down the disaccharide sucrose (regular table sugar: glucose + fructose), lactose (milk sugar: glucose + galactose), and maltose (grain sugar: glucose + glucose), and the polysaccharides glycogen and starch (chains of monosaccharides). Your bodies do not produce enzymes that can break down most fibrous polysaccharides, such as cellulose. While indigestible polysaccharides do not provide any nutritional value, they do provide dietary fiber, which helps propel food through the alimentary canal.

The chemical digestion of starches begins in the mouth and has been reviewed above.

In the small intestine, **pancreatic amylase** does the 'heavy lifting' for starch and carbohydrate digestion ([link]). After amylases break down starch into smaller fragments, the brush border enzyme α -dextrinase starts working on

 α -dextrin, breaking off one glucose unit at a time. Three brush border enzymes hydrolyze sucrose, lactose, and maltose into monosaccharides. **Sucrase** splits sucrose into one molecule of fructose and one molecule of glucose; **maltase** breaks down maltose and maltotriose into two and three glucose molecules, respectively; and **lactase** breaks down lactose into one molecule of glucose and one molecule of galactose. Insufficient lactase can lead to lactose intolerance.

Carbohydrate Digestion Flow Chart



Carbohydrates are broken down into their monomers in a series of steps.

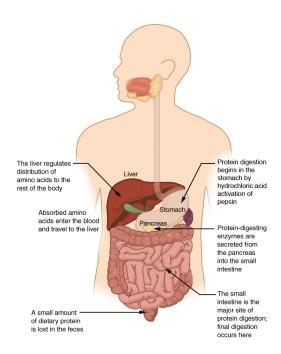
Protein Digestion

Proteins are polymers composed of amino acids linked by peptide bonds to form long chains. Digestion reduces them to their constituent amino acids. You usually consume about 15 to 20 percent of your total calorie intake as protein.

Proteases are enzymes responsible for the breakdown of proteins. The product of these proteases is dependent on the type of protease. Proteins can be grouped into two cases: 1) endopeptidases and 2) exopeptidases. Endopeptidases include pepsin, trypsin, and chymotrypsin. When these enzymes catalyze the breakdown of a protein the end result is a small peptide. This is because the endopeptidases cleave proteins at interior peptide bonds. Exopeptidases include carboxypeptidase and aminopeptidase. These enzymes cleave amino acids one at a time from the carboxyl end and amino end, respectively. Products of this cleavage are individual amino acids.

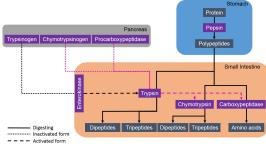
The digestion of protein starts in the stomach, where HCl and pepsin break proteins into smaller polypeptides, which then travel to the small intestine ([link]). Chemical digestion in the small intestine is continued by pancreatic enzymes, including chymotrypsin and trypsin, each of which act on specific bonds in amino acid sequences. At the same time, the cells of the brush border secrete enzymes such as **aminopeptidase** and **dipeptidase**, which further break down peptide chains. This results in molecules small enough to enter the bloodstream ([link]).

Digestion of Protein



The digestion of protein begins in the stomach and is completed in the small intestine.





Proteins are successively broken down into their amino acid components.

Lipid Digestion

A healthy diet limits lipid intake to 35 percent of total calorie intake. The most common dietary lipids are triglycerides, which are made up of a glycerol molecule bound to three fatty acid chains. Small amounts of dietary cholesterol and phospholipids are also consumed.

The three lipases responsible for lipid digestion are lingual lipase, gastric lipase, and **pancreatic lipase**. However, because the pancreas is the only consequential source of lipase, virtually all lipid digestion occurs in the small intestine. Pancreatic lipase breaks down each triglyceride into two free fatty acids and a monoglyceride. The fatty acids include both short-chain (less than 10 to 12 carbons) and long-chain fatty acids. Please remember that lipid digestion is also dependent on emulsification via bile salts in the duodenum. Lipase, however, cannot penetrate the

bile salts and as such requires an additional enzyme synthesized and secreted by the pancreas called colipase. This enzyme displaces some bile salts which allows lipase to access the fat inside the bile salt coating.

Nucleic Acid Digestion

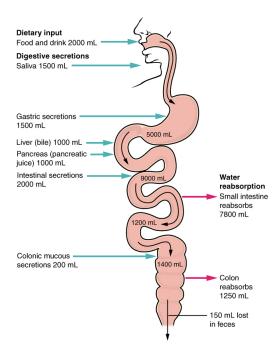
The nucleic acids DNA and RNA are found in most of the foods you eat. Two types of **pancreatic nuclease** are responsible for their digestion: **deoxyribonuclease**, which digests DNA, and **ribonuclease**, which digests RNA. The nucleotides produced by this digestion are further broken down by two intestinal brush border enzymes (**nucleosidase** and **phosphatase**) into pentoses, phosphates, and nitrogenous bases, which can be absorbed through the alimentary canal wall. The large food molecules that must be broken down into subunits are summarized [link]

Absorbable Food Substances				
Source Substance				
Carbohydrates	Monosaccharides: glucose, galactose, and fructose			
Proteins	Single amino acids, dipeptides, and tripeptides			
Triglycerides	Monoacylglycerides, glycerol, and free fatty acids			
Nucleic acids	Pentose sugars, phosphates, and nitrogenous bases			

Absorption

The mechanical and digestive processes have one goal: to convert food into molecules small enough to be absorbed by the epithelial cells of the intestinal villi. The absorptive capacity of the alimentary canal is almost endless. Each day, the alimentary canal processes up to 10 liters of food, liquids, and GI secretions, yet less than one liter enters the large intestine. Almost all ingested food, 80 percent of electrolytes, and 90 percent of water are absorbed in the small intestine. Absorption is usually completed before the chyme has the ileum. Bile salts and vitamin B_{12} are absorbed in the terminal ileum. By the time chyme passes from the ileum into the large intestine, it is essentially indigestible food residue (mainly plant fibers like cellulose), some water, and millions of bacteria ([link]).

Digestive Secretions and Absorption of Water



Absorption is a complex process, in which nutrients from digested food are harvested.

Absorption can occur through five mechanisms: (1) active transport, (2) passive diffusion, (3) facilitated diffusion, (4) co-transport (or secondary active transport), and (5) endocytosis. As you will recall from Chapter 3, active transport refers to the movement of a substance across a cell membrane going from an area of lower concentration to an area of higher concentration (up the concentration gradient). In this type of transport, proteins within the cell membrane act as "pumps," using cellular energy (ATP) to move the substance. Passive diffusion refers to the movement of substances from an area of higher concentration to an area of lower concentration, while facilitated diffusion refers to the movement of substances from an area of higher to an area of lower concentration using a carrier protein in the cell membrane. Co-transport uses the movement of one molecule through the membrane from higher to lower concentration to power the movement of another from lower to higher. Finally, endocytosis is a transportation process in which the cell membrane engulfs material. It requires energy, generally in the form of ATP.

Because the cell's plasma membrane is made up of hydrophobic phospholipids, water-soluble nutrients must use transport molecules embedded in the membrane to enter cells. Moreover, substances cannot pass between the epithelial cells of the intestinal mucosa because these cells are bound together by tight junctions. Thus, substances can only enter blood capillaries by passing through the apical surfaces of epithelial cells and into the interstitial fluid. Water-soluble nutrients enter the capillary blood in the villi and travel to the liver via the hepatic portal vein.

In contrast to the water-soluble nutrients, lipid-soluble nutrients can diffuse through the plasma membrane. Once inside the cell, they are packaged for transport via the base of the cell and then enter the lacteals of the villi to be transported by lymphatic vessels to the systemic circulation via the thoracic duct. The absorption of most nutrients through the mucosa of the intestinal villi requires active transport fueled by ATP. The routes of absorption for each food category are summarized in [link].

Absorption in the	e Alimentary Canal

Food	Breakdown products	Absorption mechanism across the apical membrane	Absorption mechanism across the basolateral membrane	Entry to bloodstream	Destination
Carbohydrates	Glucose	Co-transport with sodium ions	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Galactose	Co-transport with sodium ions	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Fructose	Facilitated diffusion (GLUT 5 carrier)	Facilitated diffusion (GLUT 2 carrier)	Capillary blood in villi	Liver via hepatic portal vein
Protein	Amino acids	Co-transport with sodium ions	Facilitated diffusion (some books show NA-AA counter transport	Capillary blood in villi	Liver via hepatic portal vein
Protein	Di/tripeptides	Co-transport with hydrogen ions	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Long-chain fatty acids	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Exocytosis	Exocytosis Lacteals of villi	
Lipids	ls Monoacylglycerides		Exocytosis Lacteals of villi		Systemic circulation via lymph entering thoracic duct

Carbohydrate Absorption

All carbohydrates are absorbed in the form of monosaccharides. The small intestine is highly efficient at this, absorbing monosaccharides at an estimated rate of 120 grams per hour. All normally digested dietary carbohydrates are absorbed; indigestible fibers are eliminated in the feces. The monosaccharides glucose and galactose are transported into the epithelial cells by common protein carriers via secondary active transport (that is, co-transport with sodium ions). The monosaccharides leave these cells via facilitated diffusion and enter the capillaries through intercellular clefts. The monosaccharide fructose (which is in fruit) is absorbed and transported by facilitated diffusion alone. The monosaccharides combine with the transport proteins immediately after the disaccharides are broken down.

Protein Absorption

Active transport mechanisms, primarily in the duodenum and jejunum, absorb most proteins as their breakdown products, amino acids. Almost all (95 to 98 percent) protein is digested and absorbed in the small intestine. The type of carrier that transports an amino acid varies. Most carriers are linked to the active transport of sodium. Short chains of two amino acids (dipeptides) or three amino acids (tripeptides) are also transported actively. However, after they enter the absorptive epithelial cells, they are broken down into their amino acids before leaving the cell and entering the capillary blood via diffusion.

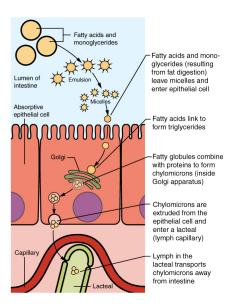
Lipid Absorption

About 95 percent of lipids are absorbed in the small intestine. Bile salts not only speed up lipid digestion, they are also essential to the absorption of the end products of lipid digestion. Short-chain fatty acids are relatively water soluble and can enter the absorptive cells (enterocytes) directly. Despite being hydrophobic, the small size of short-chain fatty acids enables them to be absorbed by enterocytes via simple diffusion, and then take the same path as monosaccharides and amino acids into the blood capillary of a villus.

The large and hydrophobic long-chain fatty acids and monoacylglycerides are not so easily suspended in the watery intestinal chyme. However, bile salts and lecithin resolve this issue by enclosing them in a **micelle**, which is a tiny sphere with polar (hydrophilic) ends facing the watery environment and hydrophobic tails turned to the interior, creating a receptive environment for the long-chain fatty acids. The core also includes cholesterol and fatsoluble vitamins. Without micelles, lipids would sit on the surface of chyme and never come in contact with the absorptive surfaces of the epithelial cells. Micelles can easily squeeze between microvilli and get very near the luminal cell surface. At this point, lipid substances exit the micelle and are absorbed via simple diffusion.

The free fatty acids and monoacylglycerides that enter the epithelial cells are reincorporated into triglycerides. The triglycerides are mixed with phospholipids and cholesterol, and surrounded with a protein coat. This new complex, called a **chylomicron**, is a water-soluble lipoprotein. After being processed by the Golgi apparatus, chylomicrons are released from the cell ([link]). Too big to pass through the basement membranes of blood capillaries, chylomicrons instead enter the large pores of lacteals. The lacteals come together to form the lymphatic vessels. The chylomicrons are transported in the lymphatic vessels and empty into the venous system via the subclavian vein. Once in the bloodstream, the enzyme **lipoprotein lipase** breaks down the triglycerides of the chylomicrons into free fatty acids and glycerol. These breakdown products then pass through capillary walls to be used for energy by cells or stored in adipose tissue as fat. Liver cells combine the remaining chylomicron remnants with proteins, forming lipoproteins that transport cholesterol in the blood.

Lipid Absorption



Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells.

Nucleic Acid Absorption

The products of nucleic acid digestion—pentose sugars, nitrogenous bases, and phosphate ions—are transported by carriers across the villus epithelium via active transport. These products then enter the bloodstream.

Mineral Absorption

The electrolytes absorbed by the small intestine are from both GI secretions and ingested foods. Since electrolytes dissociate into ions in water, most are absorbed via active transport throughout the entire small intestine. During absorption, co-transport mechanisms result in the accumulation of sodium ions inside the cells, whereas anti-port mechanisms reduce the potassium ion concentration inside the cells. To restore the sodium-potassium gradient across the cell membrane, a sodium-potassium pump requiring ATP pumps sodium out and potassium in. The mechanism for sodium absorption varies depending on the region of the intestine. In the duodenum and jejunum, sodium is absorbed via paracellular transport (between epithelial cells). This keeps sodium concentration low within enterocytes and therefore allows sodium to cross the apical membrane via co-transport with other molecules or counter transport with hydrogen ions in the jejunum, ileum, and colon. In other areas, sodium follows water absorption in a process called solvent drag.

Chloride ions have a negative charge and is therefore coupled with sodium absorption. Chloride follows sodium absorption in the jejunum. However, in the ileum and colon, chloride ions are absorbed by counter transport with bicarbonate across the apical membrane but facilitated diffusion across the basolateral membrane.

The absorption of potassium is dependent on its concentration in the lumen. If the concentration is greater than 25mM, potassium is absorbed paracellularly. If the concentration is 25mM or less, potassium ion is secreted. When diarrhea occurs, the potassium ion concentration declines in the lumen, and less potassium is absorbed leading to a state of hypokalemia.

In general, all minerals that enter the intestine are absorbed, whether you need them or not. Iron and calcium are exceptions; they are absorbed in the duodenum in amounts that meet the body's current requirements, as follows:

Iron—The ionic iron needed for the production of hemoglobin is absorbed into mucosal cells via active transport. Once inside mucosal cells, ionic iron binds to the protein ferritin, creating iron-ferritin complexes that store iron until needed. When the body has enough iron, most of the stored iron is lost when worn-out epithelial cells slough off. When the body needs iron because, for example, it is lost during acute or chronic bleeding, there is increased uptake of iron from the intestine and accelerated release of iron into the bloodstream. Since women experience significant iron loss during menstruation, they have around four times as many iron transport proteins in their intestinal epithelial cells as do men.

Calcium—Calcium is actively absorbed in the duodenum and jejunum. Calcium binds to a brush border protein called calcium binding protein and is then transported into the epithelial cell. Calcium is then transported across the basolateral membrane and into the plasma via a calcium pump. This absorption is regulated by vitamin D. Hormones also play a role in calcium absorption. When blood levels of ionic calcium drop, parathyroid hormone (PTH) secreted by the parathyroid glands stimulates the release of calcium ions from bone matrices and increases the reabsorption of calcium by the kidneys. PTH also upregulates the activation of vitamin D in the kidney, which then facilitates intestinal calcium ion absorption.

Vitamin Absorption

The small intestine absorbs the vitamins that occur naturally in food and supplements. The mechanism for absorption depends on whether the vitamin is lipophilic or lipophobic. Fat-soluble vitamins (A, D, E, and K) are absorbed along with dietary lipids in micelles and chylomicrons via simple diffusion. This is why you are advised to eat some fatty foods when you take fat-soluble vitamin supplements. Water-soluble vitamins (including most B vitamins and vitamin C) also are absorbed by special transport proteins. Some hydrophilic vitamins require active transport while others require facilitated diffusion. An exception is vitamin B_{12} , which is a very large molecule. Intrinsic factor secreted in the stomach binds to vitamin B_{12} , preventing its digestion and creating a complex that binds to mucosal receptors in the terminal ileum, where it is taken up by endocytosis.

Water Absorption

Each day, about nine liters of fluid enter the small intestine. About 2.3 liters are ingested in foods and beverages, and the rest is from GI secretions. About 90 percent of this water is absorbed in the small intestine. Water absorption is driven by the concentration gradient of the water: The concentration of water is higher in chyme than it is in epithelial cells. Thus, water moves down its concentration gradient from the chyme into cells. As noted earlier, much of the remaining water is then absorbed in the colon.

Chapter Review

The small intestine is the site of most chemical digestion and almost all absorption. Chemical digestion breaks large food molecules down into their chemical building blocks, which can then be absorbed through the intestinal wall and into the general circulation. Intestinal brush border enzymes and pancreatic enzymes are responsible for the majority of chemical digestion. The breakdown of fat also requires bile.

Most nutrients are absorbed by transport mechanisms at the apical surface of enterocytes. Exceptions include lipids, fat-soluble vitamins, and most water-soluble vitamins. With the help of bile salts and lecithin, the dietary fats are emulsified to form micelles, which can carry the fat particles to the surface of the enterocytes. There, the micelles release their fats to diffuse across the cell membrane. The fats are then reassembled into triglycerides and mixed with other lipids and proteins into chylomicrons that can pass into lacteals. Other absorbed monomers travel from blood capillaries in the villus to the hepatic portal vein and then to the liver.

Glossary

α-dextrin

breakdown product of starch

α-dextrinase

brush border enzyme that acts on α-dextrins

aminopeptidase

brush border enzyme that acts on proteins

chylomicron

large lipid-transport compound made up of triglycerides, phospholipids, cholesterol, and proteins

deoxyribonuclease

pancreatic enzyme that digests DNA

dipeptidase

brush border enzyme that acts on proteins

lactase

brush border enzyme that breaks down lactose into glucose and galactose

lipoprotein lipase

enzyme that breaks down triglycerides in chylomicrons into fatty acids and monoglycerides

maltase

brush border enzyme that breaks down maltose and maltotriose into two and three molecules of glucose, respectively

micelle

tiny lipid-transport compound composed of bile salts and phospholipids with a fatty acid and monoacylglyceride core

nucleosidase

brush border enzyme that digests nucleotides

pancreatic amylase

enzyme secreted by the pancreas that completes the chemical digestion of carbohydrates in the small intestine

pancreatic lipase

enzyme secreted by the pancreas that participates in lipid digestion

pancreatic nuclease

enzyme secreted by the pancreas that participates in nucleic acid digestion

phosphatase

brush border enzyme that digests nucleotides

ribonuclease

pancreatic enzyme that digests RNA

sucrase

brush border enzyme that breaks down sucrose into glucose and fructose

OU Human Physiology: Regulation of Digestion By the end of this section, you will be able to:

- Compare and contrast the neural and hormonal controls involved in digestion
- Compare and contrast short and long reflexes in neuronal control of digestion
- Explain the process of deglutition including the voluntary, pharyngeal, and esophageal phases
- Describe the synthesis and secretion of saliva including its autonomic regulation
- Explain the role of the gastric hormones in regulation of gastric secretions
- Describe the mechanism for hydrochloric acid and pepsinogen synthesis and secretion
- Discuss the cephalic, gastric, and intestinal phases of gastric secretion
- Describe the mechanism for pancreatic juice and bile synthesis and secretion

In a given day, approximately 9,000 ml of fluid enter the digestive system via ingested fluids or varying secretions via accessory digestive organs, of this fluid, approximately 8,900 ml are absorbed across the gut wall and into circulation. Thus, the majority of nutrients are absorbed leaving relatively little (approximately 100 ml) to be excreted from the body. The regulation of this system is not based on maintenance of internal conditions as are most organ systems we have already discussed. The digestive system is regulated via the enteric division of the autonomic nervous system and the gastrointestinal (GI) hormones. The goal of these systems is to maintain digestive motility and secretions in efforts to maximize digestion and absorption of ingested foods. This regulation is due to both intrinsic and extrinsic control mechanisms.

Neural Controls

The walls of the alimentary canal contain a variety of sensors that help regulate digestive functions. These include mechanoreceptors, chemoreceptors, and osmoreceptors, which are capable of detecting mechanical, chemical, and osmotic stimuli, respectively from the lumen of the alimentary canal. For example, these receptors can sense when the presence of food has caused the stomach to expand, whether food particles have been sufficiently broken down, how much liquid is present, and the type of nutrients in the food (lipids, carbohydrates, and/or proteins). Stimulation of these receptors provokes an appropriate reflex that furthers the process of digestion. This may entail sending a message that activates the glands that secrete digestive juices into the lumen, or it may mean the stimulation of muscles within the alimentary canal, thereby activating peristalsis and segmentation that move food along the intestinal tract.

The walls of the entire alimentary canal are embedded with nerve plexuses that interact with the central nervous system and other nerve plexuses either within the same digestive organ or in different ones. These interactions prompt several types of reflexes. Extrinsic nerve plexuses orchestrate long reflexes, which involve the central and autonomic nervous systems and work in response to stimuli from outside the digestive system. Short reflexes, on the other hand, are orchestrated by intrinsic nerve plexuses within the alimentary canal wall and do not involve the brain. These two plexuses and their connections were introduced earlier as the enteric nervous system. Short reflexes are generated via chemoreceptors, mechanoreceptors, or osmoreceptors that activate the enteric nervous system which may coordinate local peristaltic movements and stimulate digestive secretions. Long reflexes, on the other hand, are initiated by sight, smell, and taste of food that begin with a sensory neuron delivering a signal to the medulla oblongata while the chemoreceptors, mechanoreceptors, and osmoreceptors stimulate the enteric nervous system to secrete digestive juices in preparation for incoming food.

Hormonal Controls

A variety of hormones are involved in the digestive process. The main digestive hormone synthesized and secreted by the stomach is **gastrin**, which is secreted by G-cells in response to the presence of food. More specifically, protein and protein digestion products in the stomach as well as distension of the stomach and parasympathetic nervous system will stimulate gastrin secretion. Gastrin stimulates the secretion of hydrochloric

acid by the parietal cells, secretion of pepsinogen from the chief cells, increases ileal motility and initiates mixing. Other GI hormones are produced and act upon the gut and its accessory organs. Hormones produced by the duodenum and jejunum include secretin, cholecystokinin (CCK), and glucose-dependent insulinotropic peptide (GIP). Secretin is synthesized and secreted when acids enter the duodenum. Secretin stimulates pancreatic bicarbonate secretion, bile secretion by the liver and potentiates actions of CCK on the pancreas. Cholecystokinin is synthesized and secreted when fats or protein digestion products enter the duodenum. CCK stimulates the secretion of pancreatic enzymes, contraction of the gall bladder, and inhibits gastric motility and secretion. Glucose-dependent insulinotropic peptide is synthesized and secreted when glucose, fats, or acids enter the duodenum as well as the distension of the duodenum when chyme enters the duodenum. This hormone stimulates insulin secretion and inhibits gastric secretion and motility. These digestive hormones are secreted by specialized epithelial cells, called endocrinocytes, located in the mucosal epithelium of the stomach and small intestine. When secreted these hormones enter the bloodstream, through which they can reach their target organs. **Table 8** reviews the hormones that regulate digestion.

Hormones that Regulate Digestion

Hormone	Class	Site of Synthesis and Secretion via Endocrinocytes	Stimulus for Secretion	Target	Target Cell Response	Phase of Gastric Secretion																			
	Peptide	Stemach	Amino acids and peptides in stemach; Distension	Stomach	Stimulates gastric emptying																				
				Antino acids and	Chief cells	Synthesis secretion pepsinogen																			
Gastrin				Parietal cells	Synthesis secretion HCl	Cephalic and																			
	,		of stomach; Parasympathetic Nervous System	Small Intestine	Stimulates contracting to increase iteal motility	Gastric																			
				Ileocecal Valve	Relaxes																				
				Large Intestine	Stimulates mass movement																				
			Acidic chyme in duodenum	Stomach	Inhibits pepsinogen and HCl synthesis secretion																				
					Inhibits gastric motility																				
Secretin	Peptide	Duodenum and Jejunum																					Pancreas	Stimulates bicarbonate in pancreatic juice synthesis secretion Potentiates CCK actions	Intestinal
				Liver	Stimulates bile secretion																				
				Liver and pancreas	Potentiates secretin actions																				
CCK	Peptide	Peptide Duodenum and Fatty chyme and amino acids in duodenum	amino acids in	Pancreas	Stimulates pancreatic enzymes synthesis secretion	Intestinal																			
			Gallbladder	Stimulates contraction																					
			Sphincter of Oddi	Relaxes																					
GIP	Peptide	Glucose, HCl, and pepsinogen Duodenum and fatty chyrne in Stomach synthesis secretion ptide Jejunum Distension of Inhibits gastric motility	pepsinogen	Intestinal																					
OII	1 chage		miesimai																						
			duodenum	Pancreas	Stimulates insulin synthesis secretion																				

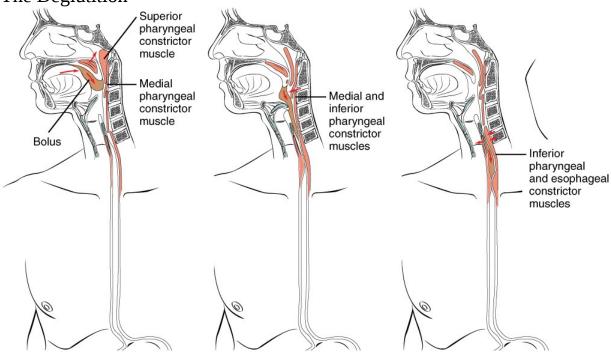
Regulation of Food Intake

Have you ever wondered why we eat? Do we eat because we are hungry or simply because the food smells good? How do we know when to stop eating? What makes us feel full? The regulation of food intake involves both short-term and long-term factors. Short-term factors include neural input from mechano- and chemoreceptors in the gut wall that detect food as well as the hormones insulin, CCK, and ghrelin. Long-term factors, on the other hand, include the leptin and other hormones.

Deglutition

Deglutition is another word for swallowing—the movement of food from the mouth to the stomach. The entire process takes about 4 to 8 seconds for solid or semisolid food, and about 1 second for very soft food and liquids. Although this sounds quick and effortless, deglutition is, in fact, a complex process that involves both the skeletal muscle of the tongue and the muscles of the pharynx and esophagus. It is aided by the presence of mucus and saliva. There are three stages in deglutition: the voluntary phase, the pharyngeal phase, and the esophageal phase ([link]). The autonomic nervous system controls the latter two phases.

The Deglutition



Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase.

The Voluntary Phase

The **voluntary phase** of deglutition (also known as the oral or buccal phase) is so called because you can control when you swallow food. In this phase, chewing has been completed and swallowing is set in motion. The

tongue moves upward and backward against the palate, pushing the bolus to the back of the oral cavity and into the oropharynx. Other muscles keep the mouth closed and prevent food from falling out. At this point, the two involuntary phases of swallowing begin.

The Pharyngeal Phase

In the pharyngeal phase, stimulation of receptors in the oropharynx sends impulses to the deglutition center (a collection of neurons that controls swallowing) in the medulla oblongata. Impulses are then sent back to the uvula and soft palate, causing them to move upward and close off the nasopharynx. The laryngeal muscles also constrict to prevent aspiration of food into the trachea. At this point, deglutition apnea takes place, which means that breathing ceases for a very brief time. Contractions of the pharyngeal constrictor muscles move the bolus through the oropharynx and laryngopharynx. Relaxation of the upper esophageal sphincter then allows food to enter the esophagus.

The Esophageal Phase

The entry of food into the esophagus marks the beginning of the esophageal phase of deglutition and the initiation of peristalsis. As in the previous phase, the complex neuromuscular actions are controlled by the medulla oblongata. Peristalsis propels the bolus through the esophagus and toward the stomach. The circular muscle layer of the muscularis contracts, pinching the esophageal wall and forcing the bolus forward. At the same time, the longitudinal muscle layer of the muscularis also contracts, shortening this area and pushing out its walls to receive the bolus. In this way, a series of contractions keeps moving food toward the stomach. When the bolus nears the stomach, distention of the esophagus initiates a short reflex relaxation of the lower esophageal sphincter that allows the bolus to pass into the stomach. During the esophageal phase, esophageal glands secrete mucus that lubricates the bolus and minimizes friction.

Not	te:			



Watch this <u>animation</u> to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?

Regulation of Secretions

Salivation

The autonomic nervous system regulates **salivation** (the secretion of saliva). In the absence of food, parasympathetic stimulation keeps saliva flowing at just the right level for comfort as you speak, swallow, sleep, and generally go about life. Over-salivation can occur, for example, if you are stimulated by the smell of food, but that food is not available for you to eat. Drooling is an extreme instance of the overproduction of saliva. During times of stress, such as before speaking in public, sympathetic stimulation takes over, reducing salivation and producing the symptom of dry mouth often associated with anxiety. When you are dehydrated, salivation is reduced, causing the mouth to feel dry and prompting you to take action to quench your thirst

Salivation can be stimulated by the sight, smell, and taste of food. It can even be stimulated by thinking about food. You might notice whether reading about food and salivation right now has had any effect on your production of saliva.

How does the salivation process work while you are eating? Food contains chemicals that stimulate taste receptors on the tongue, which send impulses to the superior and inferior salivatory nuclei in the brain stem. These two nuclei then send back parasympathetic impulses through fibers in the glossopharyngeal and facial nerves, which stimulate salivation. Even after you swallow food, salivation is increased to cleanse the mouth and to water down and neutralize any irritating chemical remnants, such as that hot sauce in your burrito. Most saliva is swallowed along with food and is reabsorbed, so that fluid is not lost.

Gastric Secretion

The cells of the stomach also play a role in the regulation of digestion. In an earlier reading you learned that both hydrochloric acid and pepsinogen are synthesized and secreted by gastric cells and their importance to gastric function. Recall that the parietal cells of the gastric pits synthesize hydrochloric acid and the chief cells synthesize and secrete pepsinogen. Watch the video to learn about the mechanism of hydrochloric acid and pepsinogen synthesis and secretion.

Gastric secretions are regulated via nerves and hormones. There are three phases for regulation: cephalic, gastric, and intestinal ([link]). Each phase is named based on where the stimuli originate. If the stimuli originate in the head, the phase of regulation is called the cephalic phase. If the stimuli originate in the stomach or intestines these phases of regulation are called gastric and intestinal, respectively. Once gastric secretion begins, all three phases can occur simultaneously.

The Three Phases of Gastric Secretion

Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.

The **cephalic phase** (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The **gastric phase** of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

The **intestinal phase** of gastric secretion has both excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying. When partially digested food fills the duodenum, intestinal mucosal cells release a hormone called intestinal (enteric) gastrin, which further excites gastric juice secretion. This stimulatory activity is brief, however, because when the intestine distends with chyme, the enterogastric

reflex inhibits secretion. One of the effects of this reflex is to close the pyloric sphincter, which blocks additional chyme from entering the duodenum.

Pancreatic Secretion

Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum is detected by chemoreceptors which generate both long and short term reflexes that stimulate the release of secretin from the endocrine cells of the duodenum and jejunum, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. When pancreatic juice enters the duodenum, it will neutralize the acidic chyme.

The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the pancreatic acini to secrete enzyme-rich pancreatic juice, contract the gall bladder, and relax the sphincter of Oddi. The contracted gall bladder will allow for the release of bile from the gall bladder while the relaxed sphincter of Oddi will allow the bile to enter the duodenum to emulsify fat and will allow for pancreatic juice to enter the duodenum to digest chyme. Thus, CCK enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the secretion of pancreatic juice.

Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

Chapter Review

The digestive system is regulated via the enteric division of the autonomic nervous system and the gastrointestinal (GI) hormones. The goal of these systems is to maintain digestive motility and secretions in efforts to

maximize digestion and absorption of ingested foods. The enteric nervous system is involved in both short and long reflexes which are activated via chemoreceptors, mechanoreceptors, or osmoreceptors. When activated these reflexes coordinate local peristaltic movements and stimulate digestive secretions. The enteric nervous system works in conjunction with the GI hormones. There are several hormones that are synthesized and secreted within the gastrointestinal tract that aid in the digestive process. Together the enteric nervous system and GI hormones regulate digestion in three phases: cephalic, gastric, and intestinal.

Glossary

cephalic phase

(also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach

cholecystokinin (CCK)

hormone synthesized and secreted by endocrine cells of the small intestine and stimulates contraction of the gall bladder, secretion of pancreatic enzymes, inhibits gastric motility and secretion, relaxes the sphincter of Oddi, and potentiates the actions of secretin

deglutition

three-stage process of swallowing

gastric phase

phase of gastric secretion that begins when food enters the stomach

gastrin

peptide hormone that stimulates secretion of hydrochloric acid and gut motility

glucose-dependent insulinotropic peptide (GIP)

hormone synthesized and secreted by endocrine cells of the small intestine and inhibits gastric secretions from the parietal and chief cells, inhibits gastric motility, and stimulates insulin secretion

intestinal phase

phase of gastric secretion that begins when chyme enters the intestine

salivation

secretion of saliva

secretin

hormone synthesized and secreted by endocrine cells of the small intestine and stimulates bicarbonate secretion from the pancreas, bile release from the gall bladder, potentiates the actions of cholecystokinin on the pancreas, and inhibits gastric secretions from the chief and parietal cells

voluntary phase

initial phase of deglutition, in which the bolus moves from the mouth to the oropharynx

OU Human Physiology: Metabolism Introduction class="introduction"
Metabolism

Metabolism is the sum of all energy-requiring and energy-consuming processes of the body.

Many factors contribute to overall metabolism, including lean muscle mass, the amount and quality of food consumed, and the physical demands placed on the human body. (credit: "tableatny"/flickr.com



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the processes and hormones involved in anabolic and catabolic reactions
- \bullet Explain oxidation-reduction reactions particularly those involving NADH2 and FADH2
- List and describe the steps necessary for carbohydrate, lipid, and protein metabolism
- Explain the processes that regulate glucose levels during the absorptive and postabsorptive states

Eating is essential to life. Many of us look to eating as not only a necessity, but also a pleasure. You may have been told since childhood to start the day

with a good breakfast to give you the energy to get through most of the day. You most likely have heard about the importance of a balanced diet, with plenty of fruits and vegetables. But what does this all mean to your body and the physiological processes it carries out each day? You need to absorb a range of nutrients so that your cells have the building blocks for metabolic processes that release the energy for the cells to carry out their daily jobs, to manufacture new proteins, cells, and body parts, and to recycle materials in the cell.

This chapter will take you through some of the chemical reactions essential to life, the sum of which is referred to as metabolism. The focus of these discussions will be anabolic reactions and catabolic reactions. You will examine the various chemical reactions that are important to sustain life, including why you must have oxygen, how mitochondria transfer energy, and the importance of certain "metabolic" hormones and vitamins.

Metabolism varies, depending on age, gender, activity level, fuel consumption, and lean body mass. Your own metabolic rate fluctuates throughout life. By modifying your diet and exercise regimen, you can increase both lean body mass and metabolic rate. Factors affecting metabolism also play important roles in controlling muscle mass. Aging is known to decrease the metabolic rate by as much as 5 percent per year. Additionally, because men tend have more lean muscle mass then women, their basal metabolic rate (metabolic rate at rest) is higher; therefore, men tend to burn more calories than women do. Lastly, an individual's inherent metabolic rate is a function of the proteins and enzymes derived from their genetic background. Thus, your genes play a big role in your metabolism. Nonetheless, each person's body engages in the same overall metabolic processes.

OU Human Physiology: Overview of Metabolic Reactions By the end of this section, you will be able to:

- Describe the process by which polymers are broken down into monomers
- Describe the process by which monomers are combined into polymers
- Discuss the role of ATP in metabolism
- Explain oxidation-reduction reactions
- Compare and contrast oxidation-reduction reactions for NADH₂ and FADH₂
- Describe the hormones that regulate anabolic and catabolic reactions

Metabolic processes are constantly taking place in the body. **Metabolism** is the sum of all of the chemical reactions that are involved in catabolism and anabolism. The reactions governing the breakdown of food to obtain energy are called catabolic reactions. Conversely, anabolic reactions use the energy produced by catabolic reactions to synthesize larger molecules from smaller ones, such as when the body forms proteins by stringing together amino acids. Both sets of reactions are critical to maintaining life.

Because catabolic reactions produce energy and anabolic reactions use energy, ideally, energy usage would balance the energy produced. If the net energy change is positive (catabolic reactions release more energy than the anabolic reactions use), then the body stores the excess energy by building fat molecules for long-term storage. On the other hand, if the net energy change is negative (catabolic reactions release less energy than anabolic reactions use), the body uses stored energy to compensate for the deficiency of energy released by catabolism.

Catabolic Reactions

Catabolic reactions break down large organic molecules into smaller molecules, releasing the energy contained in the chemical bonds. These energy releases (conversions) are not 100 percent efficient. The amount of energy released is less than the total amount contained in the molecule. Approximately 40 percent of energy yielded from catabolic reactions is directly transferred to the high-energy molecule adenosine triphosphate

(ATP). ATP, the energy currency of cells, can be used immediately to power molecular machines that support cell, tissue, and organ function. This includes building new tissue and repairing damaged tissue. ATP can also be stored to fulfill future energy demands. The remaining 60 percent of the energy released from catabolic reactions is given off as heat, which tissues and body fluids absorb.

Structurally, ATP molecules consist of an adenine, a ribose, and three phosphate groups ($[\underline{link}]$). The chemical bond between the second and third phosphate groups, termed a high-energy bond, represents the greatest source of energy in a cell. It is the first bond that catabolic enzymes break when cells require energy to do work. The products of this reaction are a molecule of adenosine diphosphate (ADP) and a lone phosphate group (P_i). ATP, ADP, and P_i are constantly being cycled through reactions that build ATP and store energy, and reactions that break down ATP and release energy.

Structure of ATP Molecule

High-energy bond 0 Adenine CH_2 **-**0 0 Energy Ribos required Catabolic reactions Anabolic reactions release energy to be store energy released used in an anabolic from a catabolic reaction Adenine -0 CH₂ 0 Ribose Energy 444 Adenine group released

ATP
Adenosine triphosphate

Adenosine triphosphate (ATP) is the energy molecule of the cell. During catabolic reactions, ATP is created and energy is

ADP
Adenosine diphosphate

Ribose

Phosphate groups

stored until needed during anabolic reactions.

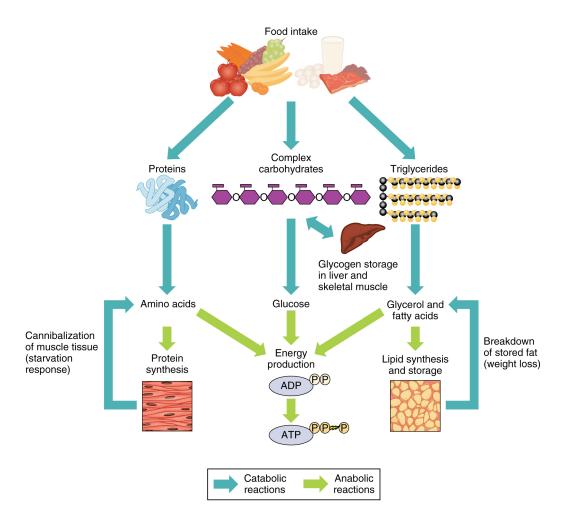
The energy from ATP drives all bodily functions, such as contracting muscles, maintaining the electrical potential of nerve cells, and absorbing food in the gastrointestinal tract. The metabolic reactions that produce ATP come from various sources ([link]).

Note:



Watch this <u>video</u> to learn more about adenosine triphosphate (ATP).

Sources of ATP



During catabolic reactions, proteins are broken down into amino acids, lipids are broken down into fatty acids, and polysaccharides are broken down into monosaccharides. These building blocks are then used for the synthesis of molecules in anabolic reactions.

Of the four major macromolecular groups (carbohydrates, lipids, proteins, and nucleic acids) that are processed by digestion, carbohydrates are considered the most common source of energy to fuel the body. They take the form of either complex carbohydrates, polysaccharides like starch and glycogen, or simple sugars (monosaccharides) like glucose and fructose. Sugar catabolism breaks polysaccharides down into their individual monosaccharides. Among the monosaccharides, glucose is the most

common fuel for ATP production in cells, and as such, there are a number of endocrine control mechanisms to regulate glucose concentration in the bloodstream. Excess glucose is either stored as an energy reserve in the liver and skeletal muscles as the complex polymer glycogen, or it is converted into fat (triglyceride) in adipose cells (adipocytes).

Among the lipids (fats), triglycerides are most often used for energy via a metabolic process called β -oxidation. About one-half of excess fat is stored in adipocytes that accumulate in the subcutaneous tissue under the skin, whereas the rest is stored in adipocytes in other tissues and organs.

Proteins, which are polymers, can be broken down into their monomers, individual amino acids. Amino acids can be used as building blocks of new proteins or broken down further for the production of ATP. When one is chronically starving, this use of amino acids for energy production can lead to a wasting away of the body, as more and more proteins are broken down.

Nucleic acids are present in most of the foods you eat. During digestion, nucleic acids including DNA and various RNAs are broken down into their constituent nucleotides. These nucleotides are readily absorbed and transported throughout the body to be used by individual cells during nucleic acid metabolism.

Anabolic Reactions

In contrast to catabolic reactions, **anabolic reactions** involve the joining of smaller molecules into larger ones. Anabolic reactions combine monosaccharides to form polysaccharides, fatty acids to form triglycerides, amino acids to form proteins, and nucleotides to form nucleic acids. These processes require energy in the form of ATP molecules generated by catabolic reactions. Anabolic reactions, also called **biosynthesis reactions**, create new molecules that form new cells and tissues, and revitalize organs.

Hormonal Regulation of Metabolism

Catabolic and anabolic hormones in the body help regulate metabolic processes. **Catabolic hormones** stimulate the breakdown of molecules and

the production of energy. These include cortisol, glucagon, adrenaline/epinephrine, and cytokines. All of these hormones are mobilized at specific times to meet the needs of the body. **Anabolic hormones** are required for the synthesis of molecules and include growth hormone, insulin-like growth factor, insulin, testosterone, and estrogen. [link] summarizes the function of each of the catabolic hormones and [link] summarizes the functions of the anabolic hormones. Please note that not all of the information in these tables may be clear to you at this point in your studies. The information will be much clearer after we study the Endocrine and Nervous systems.

Catabolic Hormones	
Hormone	Function
Cortisol	Released from the adrenal gland in response to stress; its main role is to increase blood glucose levels by gluconeogenesis (breaking down fats and proteins)
Glucagon	Released from alpha cells in the pancreas either when starving or when the body needs to generate additional energy; it stimulates the breakdown of glycogen in the liver to increase blood glucose levels; its effect is the opposite of insulin; glucagon and insulin are a part of a negative-feedback system that stabilizes blood glucose levels

Catabolic Hormones		
Hormone	Function	
Adrenaline/epinephrine	Released in response to the activation of the sympathetic nervous system; increases heart rate and heart contractility, constricts blood vessels, is a bronchodilator that opens (dilates) the bronchi of the lungs to increase air volume in the lungs, and stimulates gluconeogenesis	

Anabolic Hormones		
Hormone	Function	
Growth hormone (GH)	Synthesized and released from the pituitary gland; stimulates the growth of cells, tissues, and bones	
Insulin-like growth factor (IGF)	Stimulates the growth of muscle and bone while also inhibiting cell death (apoptosis)	

Anabolic Hormones	
Hormone	Function
Insulin	Produced by the beta cells of the pancreas; plays an essential role in carbohydrate and fat metabolism, controls blood glucose levels, and promotes the uptake of glucose into body cells; causes cells in muscle, adipose tissue, and liver to take up glucose from the blood and store it in the liver and muscle as glucagon; its effect is the opposite of glucagon; glucagon and insulin are a part of a negative-feedback system that stabilizes blood glucose levels
Testosterone	Produced by the testes in males and the ovaries in females; stimulates an increase in muscle mass and strength as well as the growth and strengthening of bone
Estrogen	Produced primarily by the ovaries, it is also produced by the liver and adrenal glands; its anabolic functions include increasing metabolism and fat deposition

Note:

Disorders of the...

Metabolic Processes: Cushing Syndrome and Addison's Disease

As might be expected for a fundamental physiological process like metabolism, errors or malfunctions in metabolic processing lead to a pathophysiology or—if uncorrected—a disease state. Metabolic diseases are most commonly the result of malfunctioning proteins or enzymes that are critical to one or more metabolic pathways. Protein or enzyme malfunction can be the consequence of a genetic alteration or mutation. However, normally functioning proteins and enzymes can also have

deleterious effects if their availability is not appropriately matched with metabolic need. For example, excessive production of the hormone cortisol (see [link]) gives rise to Cushing syndrome. Clinically, Cushing syndrome is characterized by rapid weight gain, especially in the trunk and face region, depression, and anxiety. It is worth mentioning that tumors of the pituitary that produce adrenocorticotropic hormone (ACTH), which subsequently stimulates the adrenal cortex to release excessive cortisol, produce similar effects. This indirect mechanism of cortisol overproduction is referred to as Cushing disease.

Patients with Cushing syndrome can exhibit high blood glucose levels and are at an increased risk of becoming obese. They also show slow growth, accumulation of fat between the shoulders, weak muscles, bone pain (because cortisol causes proteins to be broken down to make glucose via gluconeogenesis), and fatigue. Other symptoms include excessive sweating (hyperhidrosis), capillary dilation, and thinning of the skin, which can lead to easy bruising. The treatments for Cushing syndrome are all focused on reducing excessive cortisol levels. Depending on the cause of the excess, treatment may be as simple as discontinuing the use of cortisol ointments. In cases of tumors, surgery is often used to remove the offending tumor. Where surgery is inappropriate, radiation therapy can be used to reduce the size of a tumor or ablate portions of the adrenal cortex. Finally, medications are available that can help to regulate the amounts of cortisol. Insufficient cortisol production is equally problematic. Adrenal insufficiency, or Addison's disease, is characterized by the reduced production of cortisol from the adrenal gland. It can result from malfunction of the adrenal glands—they do not produce enough cortisol or it can be a consequence of decreased ACTH availability from the pituitary. Patients with Addison's disease may have low blood pressure, paleness, extreme weakness, fatigue, slow or sluggish movements, lightheadedness, and salt cravings due to the loss of sodium and high blood potassium levels (hyperkalemia). Victims also may suffer from loss of appetite, chronic diarrhea, vomiting, mouth lesions, and patchy skin color. Diagnosis typically involves blood tests and imaging tests of the adrenal and pituitary glands. Treatment involves cortisol replacement therapy, which usually must be continued for life.

Oxidation-Reduction Reactions

The chemical reactions underlying metabolism involve the transfer of electrons from one compound to another by processes catalyzed by enzymes. The electrons in these reactions commonly come from hydrogen atoms, which consist of an electron and a proton. A molecule gives up a hydrogen atom, in the form of a hydrogen ion (H⁺) and an electron, breaking the molecule into smaller parts. The loss of an electron, or **oxidation**, releases a small amount of energy; both the electron and the energy are then passed to another molecule in the process of **reduction**, or the gaining of an electron. These two reactions always happen together in an **oxidation-reduction reaction** (also called a redox reaction)—when an electron is passed between molecules, the donor is oxidized and the recipient is reduced. To help you remember which is which—remember the acronym OIL RIG (Oxidized Is Losing, Reduced Is Gained). Oxidationreduction reactions often happen in a series, so that a molecule that is reduced is subsequently oxidized, passing on not only the electron it just received but also the energy it received. As the series of reactions progresses, energy accumulates that is used to combine P_i and ADP to form ATP, the high-energy molecule that the body uses for fuel.

Oxidation-reduction reactions are catalyzed by enzymes that trigger the removal of hydrogen atoms. Coenzymes work with enzymes and accept hydrogen atoms. The two most common coenzymes of oxidation-reduction reactions are **nicotinamide adenine dinucleotide (NAD)** and **flavin adenine dinucleotide (FAD)**. Their respective reduced coenzymes are **NADH** and **FADH**₂, which are energy-containing molecules used to transfer energy during the creation of ATP.

NAD⁺ and FAD⁺ Oxidation-Reduction Reactions

a.

$$O = P - O$$

$$H = P - O$$

 $\mathbf{NAD}^{\scriptscriptstyle +}$ and $\mathbf{FAD}^{\scriptscriptstyle +}$ are coenzymes that are used to transfer energy via oxidation-reduction reactions to create ATP.

FADH₂

Chapter Review

FAD+ + 2H+ + 2e-

Metabolism is the sum of all catabolic (break down) and anabolic (synthesis) reactions in the body. The metabolic rate measures the amount of energy used to maintain life. An organism must ingest a sufficient amount of food to maintain its metabolic rate if the organism is to stay alive for very long.

Catabolic reactions break down larger molecules, such as carbohydrates, lipids, and proteins from ingested food, into their constituent smaller parts. They also include the breakdown of ATP, which releases the energy needed for metabolic processes in all cells throughout the body.

Anabolic reactions, or biosynthetic reactions, synthesize larger molecules from smaller constituent parts, using ATP as the energy source for these reactions. Anabolic reactions build bone, muscle mass, and new proteins, fats, and nucleic acids. Oxidation-reduction reactions transfer electrons across molecules by oxidizing one molecule and reducing another, and collecting the released energy to convert P_i and ADP into ATP. Errors in metabolism alter the processing of carbohydrates, lipids, proteins, and nucleic acids, and can result in a number of disease states.

Glossary

anabolic hormones

hormones that stimulate the synthesis of new, larger molecules

anabolic reactions

reactions that build smaller molecules into larger molecules

biosynthesis reactions

reactions that create new molecules, also called anabolic reactions

catabolic hormones

hormones that stimulate the breakdown of larger molecules

catabolic reactions

reactions that break down larger molecules into their constituent parts

FADH₂

high-energy molecule needed for glycolysis

flavin adenine dinucleotide (FAD) coenzyme used to produce FADH₂

metabolism

sum of all catabolic and anabolic reactions that take place in the body

NADH

high-energy molecule needed for glycolysis

nicotinamide adenine dinucleotide (NAD) coenzyme used to produce NADH

oxidation

loss of an electron

oxidation-reduction reaction

(also, redox reaction) pair of reactions in which an electron is passed from one molecule to another, oxidizing one and reducing the other

reduction

gaining of an electron

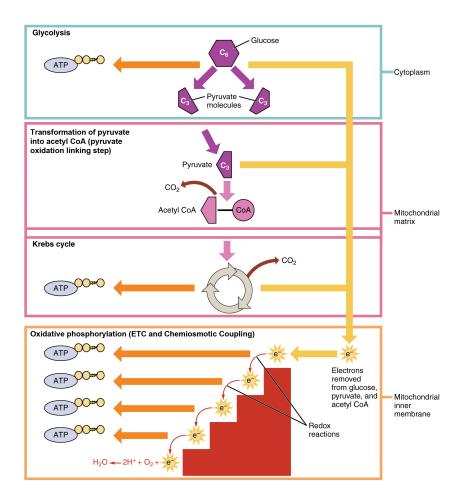
OU Human Physiology: Carbohydrate Metabolism By the end of this section, you will be able to:

- Explain the processes of glycolysis
- Describe the pathway of a pyruvate molecule through the Krebs cycle
- Explain the transport of electrons through the electron transport chain
- Describe the process of ATP production through oxidative phosphorylation and chemiosmotic coupling
- Compare and contrast the location and inputs and output for glycolysis, pyruvate oxidation, Krebs cycle, and oxidative phosphorylation
- Summarize the process of gluconeogenesis

Carbohydrates are organic molecules composed of carbon, hydrogen, and oxygen atoms. The family of carbohydrates includes both simple and complex sugars. Glucose and fructose are examples of simple sugars, and starch, glycogen, and cellulose are all examples of complex sugars. The complex sugars are also called **polysaccharides** and are made of multiple **monosaccharide** molecules. Polysaccharides serve as energy storage (e.g., starch and glycogen) and as structural components (e.g., chitin in insects and cellulose in plants).

During digestion, carbohydrates are broken down into simple, soluble sugars that can be transported across the intestinal wall into the circulatory system to be transported throughout the body. Carbohydrate digestion begins in the mouth with the action of **salivary amylase** on starches and ends with monosaccharides being absorbed across the epithelium of the small intestine. Once the absorbed monosaccharides are transported to the tissues, the process of **cellular respiration** begins ([link]). This section will focus first on glycolysis, a process where the monosaccharide glucose is oxidized, releasing the energy stored in its bonds to produce ATP.

Cellular Respiration



Cellular respiration oxidizes glucose molecules through glycolysis, the Krebs cycle, and oxidative phosphorylation to produce ATP.



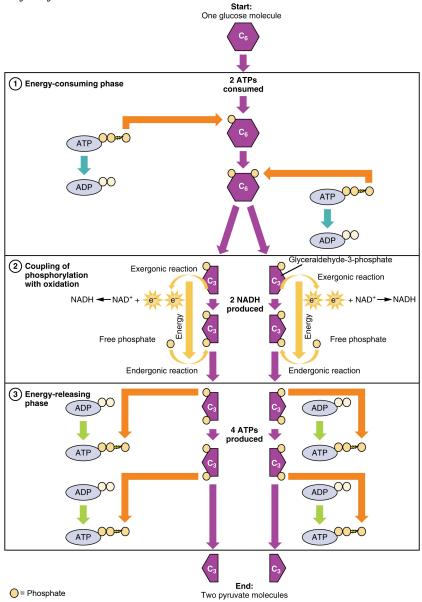


Watch this <u>video</u> to learn about cellular respiration.

Glycolysis

Glucose is the body's most readily available source of energy. After digestive processes break polysaccharides down into monosaccharides, including glucose, the monosaccharides are transported across the wall of the small intestine and into the circulatory system, which transports them to the liver. In the liver, hepatocytes either pass the glucose on through the circulatory system or store excess glucose as glycogen in a process called **glycogenesis**. Cells in the body take up the circulating glucose in response to insulin and, through a series of reactions called **glycolysis**, transfer some of the energy in glucose to ADP to form ATP ([link]). The last step in glycolysis produces the product **pyruvate**.

Glycolysis Overview

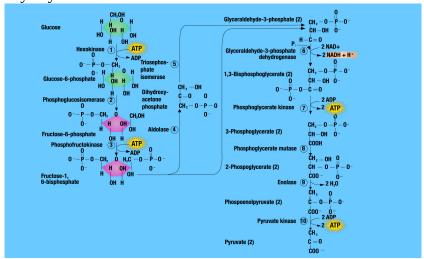


During the energy-consuming phase of glycolysis, two ATPs are consumed, transferring two phosphates to the glucose molecule. The glucose molecule then splits into two three-carbon compounds, each containing a phosphate.

During the second phase, an additional phosphate is added to each of the three-carbon compounds. The energy for this endergonic reaction is provided by the removal (oxidation) of two electrons from each three-carbon compound. During the energy-releasing phase, the phosphates are removed from both three-carbon compounds and used to produce four ATP molecules. Please note that each purple arrow indicates an enzyme catalyzed reaction.

Glycolysis begins with the phosphorylation of glucose by the enzyme hexokinase to form glucose-6-phosphate. This step uses one ATP, which is the donor of the phosphate group. Under the action of phosphofructokinase, glucose-6-phosphate is converted into fructose-6phosphate. At this point, a second ATP donates its phosphate group, forming fructose-1,6bisphosphate. This six-carbon sugar is split to form two phosphorylated three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, which are both converted into glyceraldehyde-3-phosphate. The glyceraldehyde-3-phosphate is further phosphorylated with groups donated by dihydrogen phosphate present in the cell to form the three-carbon molecule 1,3-bisphosphoglycerate. The energy of this reaction comes from the oxidation of (removal of electrons from) glyceraldehyde-3-phosphate. In a series of reactions leading to pyruvate, the two phosphate groups are then transferred to two ADPs to form two ATPs. Thus, glycolysis uses two ATPs but generates four ATPs, yielding a net gain of two ATPs and two molecules of pyruvate. In the presence of oxygen, pyruvate is oxidized (in a linking step) and then continues on to the Krebs cycle (also called the **citric acid cycle** or tricarboxylic acid cycle (TCA), where additional energy is extracted and passed on. (see [link])

Glycolysis Reactions



The glycolysis pathway including intermediates of the reaction.

Note:



Watch this <u>video</u> to learn about glycolysis.

Glycolysis can be divided into two phases: energy consuming (also called chemical priming) and energy yielding. The first phase is the **energy-consuming phase**, so it requires two ATP molecules to start the reaction for each molecule of glucose. However, the end of the reaction produces four ATPs, resulting in a net gain of two ATP energy molecules.

Glycolysis can be expressed as the following equation:

Equation:

$${
m Glucose} + 2{
m ATP} + 2{
m NAD}^+ + 4{
m ADP} + 2{
m P}_i \ o \ 2\ {
m Pyruvate} + 4{
m ATP} + 2{
m NADH} + 2{
m H}^+$$

This equation states that glucose, in combination with ATP (the energy source), NAD⁺ (a coenzyme that serves as an electron acceptor), and inorganic phosphate, breaks down into two pyruvate molecules, generating four ATP molecules—for a net yield of two ATP—and two energy-containing NADH coenzymes. The NADH that is produced in this process will be used later to produce ATP in the mitochondria. Importantly, by the end of this process, one glucose molecule generates two pyruvate molecules, two high-energy ATP molecules, and two electron-carrying NADH molecules.

The following discussions of glycolysis include the enzymes responsible for the reactions and the intermediates in the reaction. The names of the enzymes and intermediates are not important, but understanding the oxidation-reduction and hydrolysis reactions as well as the reactants and products of the overall reaction is very important. When glucose enters a cell, the enzyme hexokinase (or glucokinase, in the liver) rapidly adds a phosphate to convert it into **glucose-6-phosphate**. A kinase is a type of enzyme that adds a phosphate molecule to a substrate (in this case, glucose, but it can be true of other molecules also). This conversion step requires one ATP and essentially traps the glucose in the cell, preventing it from passing back through the plasma membrane, thus allowing glycolysis to proceed. It also functions to maintain a concentration gradient with higher glucose levels in the blood than in the tissues. By establishing this concentration gradient, the glucose in the blood will be able to flow from an area of high concentration (the blood) into an area of low concentration (the tissues) to be either used or stored. **Hexokinase** is found in nearly every tissue in the body. **Glucokinase**, on

the other hand, is expressed in tissues that are active when blood glucose levels are high, such as the liver. Hexokinase has a higher affinity for glucose than glucokinase and therefore is able to convert glucose at a faster rate than glucokinase. This is important when levels of glucose are very low in the body, as it allows glucose to travel preferentially to those tissues that require it more.

In the next step of the first phase of glycolysis, the enzyme glucose-6-phosphate isomerase converts glucose-6-phosphate into fructose-6-phosphate. Like glucose, fructose is also a six carbon-containing sugar. The enzyme phosphofructokinase-1 then adds one more phosphate to convert fructose-6-phosphate into fructose-1-6-bisphosphate, another six-carbon sugar, using another ATP molecule. Aldolase then breaks down this fructose-1-6-bisphosphate into two three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. The triosephosphate isomerase enzyme then converts dihydroxyacetone phosphate into a second glyceraldehyde-3-phosphate molecule. Therefore, by the end of this chemical-priming or energy-consuming phase, one glucose molecule is broken down into two glyceraldehyde-3-phosphate molecules.

The second phase of glycolysis, the **energy-yielding phase**, creates the energy that is the product of glycolysis. Glyceraldehyde-3-phosphate dehydrogenase converts each three-carbon glyceraldehyde-3-phosphate produced during the energy-consuming phase into 1,3-bisphosphoglycerate. This reaction releases an electron that is then picked up by NAD⁺ to create an NADH molecule. NADH is a high-energy molecule, like ATP, but unlike ATP, it is not used as energy currency by the cell. Because there are two glyceraldehyde-3-phosphate molecules, two NADH molecules are synthesized during this step. Each 1,3-bisphosphoglycerate is subsequently dephosphorylated (i.e., a phosphate is removed) by phosphoglycerate kinase into 3-phosphoglycerate. Each phosphate released in this reaction can convert one molecule of ADP into one high-energy ATP molecule, resulting in a gain of two ATP molecules.

The enzyme phosphoglycerate mutase then converts the 3-phosphoglycerate molecules into 2-phosphoglycerate. The enolase enzyme then acts upon the 2-phosphoglycerate molecules to convert them into phosphoenolpyruvate molecules. The last step of glycolysis involves the dephosphorylation of the two phosphoenolpyruvate molecules by pyruvate kinase to create two pyruvate molecules and two ATP molecules.

In summary, glycolysis takes one glucose molecule and breaks it down into two pyruvate molecules yielding a net gain of two ATPs and two NADH molecules. Therefore, glycolysis generates energy for the cell and creates pyruvate molecules that can be oxidized and continue on to the aerobic **Krebs cycle** (also called the **citric acid cycle** or **tricarboxylic acid cycle** (TCA)); converted into lactic acid or alcohol (in yeast) by fermentation; or used later for the synthesis of glucose through gluconeogenesis.

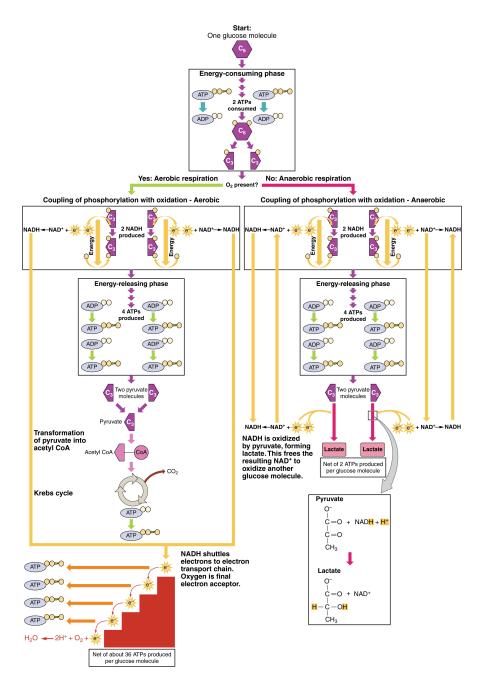
Anaerobic Respiration

When oxygen is limited or absent, pyruvate enters an anaerobic pathway. In these reactions, pyruvate can be converted into lactic acid. In addition to generating an additional ATP, this pathway serves to keep the pyruvate concentration low so glycolysis continues, and it oxidizes NADH into the NAD⁺ needed by glycolysis. In this reaction, lactic acid replaces oxygen as the final electron acceptor. Anaerobic respiration occurs in most cells of the body when oxygen is limited or mitochondria are absent or nonfunctional. For example, because erythrocytes (red blood cells) lack mitochondria, they must produce their ATP from anaerobic respiration. This is an effective pathway of ATP production for short periods of time, ranging from seconds to a few minutes. The lactic acid produced diffuses into the plasma and is carried to the liver, where it is converted back into pyruvate or glucose via the Cori cycle. Similarly, when a person exercises, muscles use ATP faster than oxygen can be delivered to them. They depend on glycolysis and lactic acid production for rapid ATP production.

Aerobic Respiration

In the presence of oxygen, pyruvate will be oxidized and can enter the Krebs cycle where additional energy is extracted as electrons are transferred from the pyruvate to the receptors NAD⁺, GDP, and FAD, with carbon dioxide being a "waste product" ([link]). The NADH and FADH₂ pass electrons on to the electron transport chain, which uses the transferred energy to produce ATP. As the terminal step in the electron transport chain, oxygen is the **terminal electron acceptor** and creates water inside the mitochondria.

Aerobic versus Anaerobic Respiration

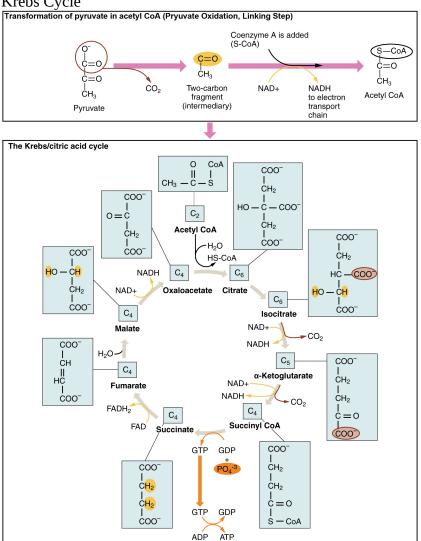


The process of anaerobic respiration converts glucose into two lactate molecules in the absence of oxygen or within erythrocytes that lack mitochondria. During aerobic respiration, glucose is oxidized into two pyruvate molecules.

Krebs Cycle

The pyruvate molecules generated during glycolysis are transported across the mitochondrial membrane into the inner mitochondrial matrix, where they are first oxidized in the linking step and then metabolized by enzymes in a pathway called the **Krebs cycle** ([link]). The Krebs cycle is also commonly called the citric acid cycle or the tricarboxylic acid (TCA) cycle. During the Krebs cycle, high-energy molecules, including ATP, NADH, and FADH₂, are created. NADH and FADH₂ then pass electrons through the electron transport chain in the mitochondria to generate more ATP molecules.

Krebs Cycle



During the Krebs cycle, each pyruvate that is generated by glycolysis is converted into a two-carbon acetyl CoA molecule. The acetyl CoA is systematically processed through the cycle and produces high-energy NADH, FADH₂, and ATP molecules. Please note that each gray arrow indicates an enzyme catalyzed reaction

Note:



Watch this <u>video</u> to learn more about the Krebs cycle.

The three-carbon pyruvate molecules generated during glycolysis move from the cytoplasm into the mitochondrial matrix, where they are converted by the enzyme pyruvate dehydrogenase into a two-carbon **acetyl coenzyme A (acetyl CoA)** molecule. This reaction is an oxidative decarboxylation reaction and is often referred to as a linking step or pyruvate oxidation. It converts each three-carbon pyruvate into a two-carbon acetyl CoA molecule, releasing carbon dioxide and transferring two electrons that combine with NAD⁺ to form NADH. Acetyl CoA enters the Krebs cycle by combining with a four-carbon molecule, oxaloacetate, to form the six-carbon molecule citrate, or citric acid, at the same time releasing the coenzyme A molecule.

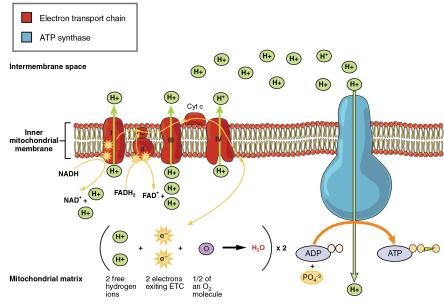
The six-carbon citrate molecule is systematically converted to a five-carbon molecule and then a four-carbon molecule, ending with oxaloacetate, the beginning of the cycle. Along the way, each citrate molecule will produce one ATP, one $FADH_2$, and three NADH. The $FADH_2$ and NADH will enter the oxidative phosphorylation system located in the inner mitochondrial membrane. In addition, the Krebs cycle supplies the starting materials to process and break down proteins and fats.

To start the Krebs cycle, citrate synthase combines acetyl CoA and oxaloacetate to form a sixcarbon citrate molecule; CoA is subsequently released and can combine with another pyruvate molecule to begin the cycle again. The aconitase enzyme converts citrate into isocitrate. In two successive steps of oxidative decarboxylation, two molecules of CO₂ and two NADH molecules are produced when isocitrate dehydrogenase converts isocitrate into the five-carbon α -ketoglutarate, which is then catalyzed and converted into the four-carbon succinyl CoA by α ketoglutarate dehydrogenase. The enzyme succinyl CoA dehydrogenase then converts succinyl CoA into succinate and forms the high-energy molecule GTP, which transfers its energy to ADP to produce ATP. Succinate dehydrogenase then converts succinate into fumarate, forming a molecule of FADH₂. Fumarase then converts fumarate into malate, which malate dehydrogenase then converts back into oxaloacetate while reducing NAD⁺ to NADH. Oxaloacetate is then ready to combine with the next acetyl CoA to start the Krebs cycle again (see [link]). For each turn of the cycle, three NADH, one ATP (through GTP), and one FADH₂ are created. Each carbon of pyruvate is converted into CO₂, which is released as a byproduct of oxidative (aerobic) respiration. Remember that for each glucose molecule, there are two pyruvates produced and therefore two turns of the Krebs cycle.

Oxidative Phosphorylation

Oxidative phosphorylation includes two parts; electron transport chain (ETC) and chemiosmotic coupling. The ETC and chemiosmotic coupling are part of oxidative phophorylation. The ETC uses electron carriers to pump protons across the cristae and into the intermembrane space. Chemiosmotic coupling then, generates ATP when protons are transported back into the matrix via ATP synthase. The **electron transport chain (ETC)** uses electrons from the oxidation of NADH (produced by glycolysis, pyruvate oxidation, and Krebs cycle) and FADH₂ (produced by Krebs cycle). These electrons are transferred through protein complexes embedded in the inner mitochondrial membrane by a series of enzymatic reactions. The electron transport chain consists of a series of four enzyme complexes (Complex I – Complex IV) and two coenzymes (ubiquinone and Cytochrome c), which act as electron carriers and proton pumps used to transfer H⁺ ions into the space between the inner and outer mitochondrial membranes ([link]). The ETC couples the transfer of electrons between a donor (like NADH and FADH₂) and an electron acceptor (like O₂) with the transfer of protons (H⁺ ions) across the inner mitochondrial membrane, enabling the process of **oxidative phosphorylation**. In the presence of oxygen, energy is passed, stepwise, through the electron carriers to collect gradually the energy needed to attach a phosphate to ADP and produce ATP. The role of molecular oxygen, O₂, is as the terminal electron acceptor for the ETC. This means that once the electrons have passed through the entire ETC, they must be passed to another, separate molecule. These electrons, O₂, and H⁺ ions from the matrix combine to form new water molecules. This is the basis for your need to breathe in oxygen. Without oxygen, electron flow through the ETC ceases.

Electron Transport Chain



The electron transport chain is a series of electron carriers and ion pumps that are used to pump H⁺ ions out of the inner mitochondrial matrix.

Note:



Watch this <u>video</u> to learn about the electron transport chain.

Note:



Watch this <u>video</u> to learn about oxidative phosphorylation and chemiosmosis.

The electrons released from NADH and FADH₂ are passed along the chain by each of the carriers, which are reduced when they receive the electron and oxidized when passing it on to the next carrier. Each of these reactions releases a small amount of energy, which is used to pump H⁺ ions across the inner membrane. The accumulation of these protons in the space between the membranes creates a proton gradient with respect to the mitochondrial matrix.

Also embedded in the inner mitochondrial membrane is an amazing protein pore complex called **ATP synthase**. Effectively, it is a turbine that is powered by the flow of H^+ ions across the inner membrane down a gradient and into the mitochondrial matrix. As the H^+ ions traverse the complex, the shaft of the complex rotates. This rotation enables other portions of ATP synthase to encourage ADP and P_i to create ATP. This process whereby ATP is produced by the transport of protons by ATP synthase is called **chemiosmosis** or chemiosmotic coupling. In accounting for the total number of ATP produced per glucose molecule through aerobic respiration, it is important to remember the following points:

- A net of two ATP are produced through glycolysis (four produced and two consumed during the energy-consuming stage).
- In all phases after glycolysis, the number of ATP, NADH, and FADH₂ produced must be multiplied by two to reflect how each glucose molecule produces two pyruvate molecules.
- In the ETC, about three ATP are produced for every oxidized NADH. However, only about two ATP are produced for every oxidized FADH2. The electrons from FADH2 produce less ATP, because they start at a lower point in the ETC (Complex II) compared to the electrons from NADH (Complex I) (see ([link])).

• The ETC and chemiosmotic coupling are part of oxidative phosphorylation. The ETC uses electron carries to pump protons across the cristae and into the intermembrane space. Chemiosmotic coupling then, generates ATP when protons are transported back into the matrix via ATP synthase.

Therefore, for every glucose molecule that enters aerobic respiration, a net total of 36 ATPs are produced ([link]).

Carbohydrate Metabolism Glycolysis Glucose C₆ 4 ATP - 2 ATP used 2 NADH Active transport of NADH from Pyruvate Transformation of pyruvate to acetyl CoA 1 NADH Pyruvate x 2 pyruvates 2 NADH CO2 Acetyl CoA Krebs cycle 3 NADH x 2 pyruvates 6 NADH x 2 pyruvates 1 FADH₂ x 2 pyruvates 2 FADH₂ Electron transport chain Electron carrier 2 FADH₂ 3 ATP x 10 NADH = 30 ATP + 2 ATP x 2 FADH₂ = 4 ATP reactions H₂O ← 2H+ + O₂ + Total ATP produced: 2 ATP –2 ATP NADH transport cost = Hypruvate into acetyl CoA = 0 ATP
Krebs cycle = 2 ATP
+ ETC = 34 ATP

Carbohydrate metabolism involves glycolysis, the Krebs cycle, and the electron transport chain. The NADH Transport cost is associated with transporting NADH produced from glycolysis into the mitochondrial matrix. The cost for this transport is two ATPs.

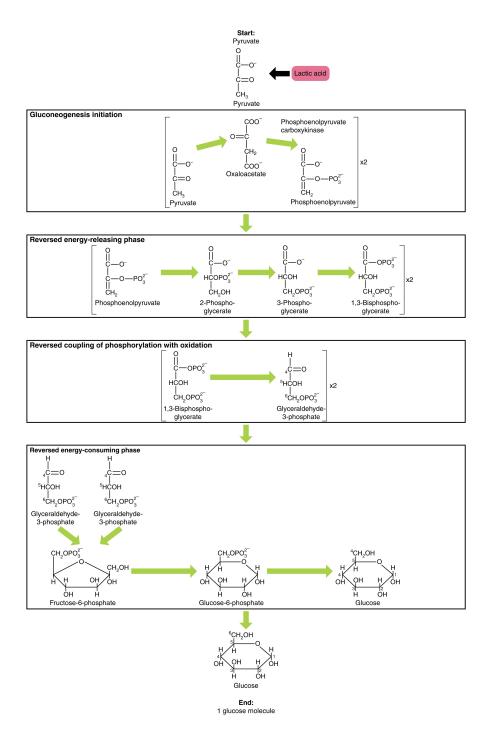
36 ATP per glucose

Gluconeogenesis

Gluconeogenesis is the synthesis of new glucose molecules from pyruvate, lactate, glycerol, or the amino acids alanine or glutamine. This process takes place primarily in the liver during periods of low glucose, that is, under conditions of fasting, starvation, and low carbohydrate diets. So, the question can be raised as to why the body would create something it has just spent a fair amount of effort to break down? Certain key organs, including the brain, can use only glucose as an energy source; therefore, it is essential that the body maintain a minimum blood glucose concentration. When the blood glucose concentration falls below that certain point, new glucose is synthesized by the liver to raise the blood concentration to normal.

Gluconeogenesis is not simply the reverse of glycolysis. There are some important differences ([link]). Pyruvate is a common starting material for gluconeogenesis. First, the pyruvate is converted into oxaloacetate. Oxaloacetate then serves as a substrate for the enzyme phosphoenolpyruvate carboxykinase (PEPCK), which transforms oxaloacetate into phosphoenolpyruvate (PEP). From this step, gluconeogenesis is nearly the reverse of glycolysis. PEP is converted back into 2-phosphoglycerate, which is converted into 3-phosphoglycerate. Then, 3-phosphoglycerate is converted into 1,3 bisphosphoglycerate and then into glyceraldehyde-3-phosphate. Two molecules of glyceraldehyde-3-phosphate then combine to form fructose-1-6-bisphosphate, which is converted into fructose 6-phosphate and then into glucose-6-phosphate. Finally, a series of reactions generates glucose itself. In gluconeogenesis (as compared to glycolysis), the enzyme hexokinase is replaced by glucose-6-phosphatase, and the enzyme phosphofructokinase-1 is replaced by fructose-1,6-bisphosphatase. This helps the cell to regulate glycolysis and gluconeogenesis independently of each other.

As will be discussed as part of lipolysis, fats can be broken down into glycerol, which can be phosphorylated to form dihydroxyacetone phosphate or DHAP. DHAP can either enter the glycolytic pathway or be used by the liver as a substrate for gluconeogenesis. Gluconeogenesis



Gluconeogenesis is the synthesis of glucose from pyruvate, lactate, glycerol, alanine, or glutamate.

Aging and the...

Body's Metabolic Rate

The human body's metabolic rate decreases nearly 2 percent per decade after age 30. Changes in body composition, including reduced lean muscle mass, are mostly responsible for this decrease. The most dramatic loss of muscle mass, and consequential decline in metabolic rate, occurs between 50 and 70 years of age. Loss of muscle mass is the equivalent of reduced strength, which tends to inhibit seniors from engaging in sufficient physical activity. This results in a positive-feedback system where the reduced physical activity leads to even more muscle loss, further reducing metabolism.

There are several things that can be done to help prevent general declines in metabolism and to fight back against the cyclic nature of these declines. These include eating breakfast, eating small meals frequently, consuming plenty of lean protein, drinking water to remain hydrated, exercising (including strength training), and getting enough sleep. These measures can help keep energy levels from dropping and curb the urge for increased calorie consumption from excessive snacking. While these strategies are not guaranteed to maintain metabolism, they do help prevent muscle loss and may increase energy levels. Some experts also suggest avoiding sugar, which can lead to excess fat storage. Spicy foods and green tea might also be beneficial. Because stress activates cortisol release, and cortisol slows metabolism, avoiding stress, or at least practicing relaxation techniques, can also help.

Chapter Review

Metabolic enzymes catalyze catabolic reactions that break down carbohydrates contained in food. The energy released is used to power the cells and systems that make up your body. Excess or unutilized energy is stored as fat or glycogen for later use. Carbohydrate metabolism begins in the mouth, where the enzyme salivary amylase begins to break down complex sugars into monosaccharides. These can then be transported across the intestinal membrane into the bloodstream and then to body tissues. In the cells, glucose, a six-carbon sugar, is processed through a sequence of reactions into smaller sugars, and the energy stored inside the molecule is released. The first step of carbohydrate catabolism is glycolysis, which produces pyruvate, NADH, and ATP. Under anaerobic conditions, the pyruvate can be converted into lactate to keep glycolysis working. Under aerobic conditions, pyruvate enters the Krebs cycle, also called the citric acid cycle or tricarboxylic acid cycle. In addition to ATP, the Krebs cycle produces high-energy FADH2 and NADH molecules, which provide electrons to the oxidative phosphorylation process that generates more high-energy ATP molecules. For each molecule of glucose that is processed in glycolysis, a net of 36 ATPs can be created by aerobic respiration.

Under anaerobic conditions, ATP production is limited to those generated by glycolysis. While a total of four ATPs are produced by glycolysis, two are needed to begin glycolysis, so there is a net yield of two ATP molecules.

In conditions of low glucose, such as fasting, starvation, or low carbohydrate diets, glucose can be synthesized from lactate, pyruvate, glycerol, alanine, or glutamate. This process, called gluconeogenesis, is almost the reverse of glycolysis and serves to create glucose molecules for glucose-dependent organs, such as the brain, when glucose levels fall below normal.

Glossary

acetyl coenzyme A (acetyl CoA) starting molecule of the Krebs cycle

ATP synthase

protein pore complex that creates ATP

cellular respiration

production of ATP from glucose oxidation via glycolysis, the Krebs cycle, and oxidative phosphorylation

citric acid cycle

also called the Krebs cycle or the tricarboxylic acid cycle; converts pyruvate into CO_2 and high-energy FADH₂, NADH, and ATP molecules

electron transport chain (ETC)

ATP production pathway in which electrons are passed through a series of oxidation-reduction reactions that forms water and produces a proton gradient

energy-consuming phase

first phase of glycolysis, in which two molecules of ATP are necessary to start the reaction

energy-yielding phase

second phase of glycolysis, during which energy is produced

glucokinase

cellular enzyme, found in the liver, which converts glucose into glucose-6-phosphate upon uptake into the cell

gluconeogenesis

process of glucose synthesis from pyruvate or other molecules

glucose-6-phosphate

phosphorylated glucose produced in the first step of glycolysis

glycolysis

series of metabolic reactions that breaks down glucose into pyruvate and produces ATP

hexokinase

cellular enzyme, found in most tissues, that converts glucose into glucose-6-phosphate upon uptake into the cell

Krebs cycle

also called the citric acid cycle or the tricarboxylic acid cycle, converts pyruvate into CO₂ and high-energy FADH₂, NADH, and ATP molecules

monosaccharide

smallest, monomeric sugar molecule

oxidative phosphorylation

process that converts high-energy NADH and FADH2 into ATP

polysaccharides

complex carbohydrates made up of many monosaccharides

pyruvate

three-carbon end product of glycolysis and starting material that is converted into acetyl CoA that enters the Krebs cycle

salivary amylase

digestive enzyme that is found in the saliva and begins the digestion of carbohydrates in the mouth

terminal electron acceptor

oxygen, the recipient of the free hydrogen at the end of the electron transport chain

tricarboxylic acid cycle (TCA)

also called the Krebs cycle or the citric acid cycle; converts pyruvate into CO_2 and high-energy $FADH_2$, NADH, and ATP molecules

OU Human Physiology: Lipid Metabolism By the end of this section, you will be able to:

- Explain how energy can be derived from fat
- Explain the purpose and process of ketogenesis
- Describe the process of ketone body oxidation
- Explain the purpose and the process of lipogenesis

Fats (or triglycerides) within the body are ingested as food or synthesized by adipocytes or hepatocytes from carbohydrate precursors ([link]). Lipid metabolism entails the oxidation of fatty acids to either generate energy or synthesize new lipids from smaller constituent molecules. Lipid metabolism is associated with carbohydrate metabolism, as products of glucose (such as acetyl CoA) can be converted into lipids.

Triglyceride Broken Down into a Monoglyceride (a) Triglyceride

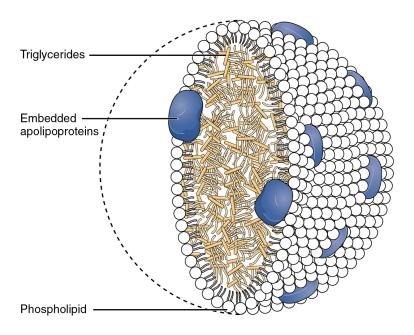
(b) Monoglyceride

A triglyceride molecule (a) breaks down into a monoglyceride (b).

Lipid metabolism begins in the intestine where ingested **triglycerides** are broken down into smaller chain fatty acids and subsequently into **monoglyceride molecules** (see [link]b) by **pancreatic lipases**, enzymes that break down fats after they are emulsified by **bile salts**. When food reaches the small intestine in the form of chyme, a digestive hormone called **cholecystokinin** (**CCK**) is released by intestinal cells in the intestinal mucosa. CCK stimulates the release of pancreatic lipase from the pancreas and stimulates the contraction of the gallbladder to release stored bile salts into the intestine. CCK also travels to the brain, where it can act as a hunger suppressant.

Together, the pancreatic lipases and bile salts break down triglycerides into free fatty acids. These fatty acids can be transported across the intestinal membrane. However, once they cross the membrane, they are recombined to again form triglyceride molecules. Within the intestinal cells, these triglycerides are packaged along with cholesterol molecules in phospholipid vesicles called **chylomicrons** ([link]). The chylomicrons enable fats and cholesterol to move within the aqueous environment of your lymphatic and circulatory systems. Chylomicrons leave the enterocytes by exocytosis and enter the lymphatic system via lacteals in the villi of the intestine. From the lymphatic system, the chylomicrons are transported to the circulatory system. Once in the circulation, they can either go to the liver or be stored in fat cells (adipocytes) that comprise adipose (fat) tissue found throughout the body.

Chylomicrons



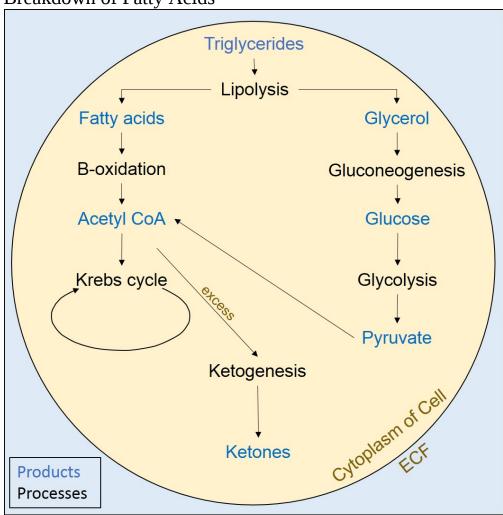
Chylomicrons contain triglycerides, cholesterol molecules, and other apolipoproteins (protein molecules). They function to carry these water-insoluble molecules from the intestine, through the lymphatic system, and into the bloodstream, which carries the lipids to adipose tissue for storage.

Lipolysis

To obtain energy from fat, triglycerides must first be broken down by hydrolysis into their two principal components, fatty acids and glycerol. This process, called **lipolysis**, takes place in the cytoplasm. The resulting fatty acids are oxidized by β -oxidation or fatty acid oxidation into acetyl CoA, which is used by the Krebs cycle ([link]). The glycerol that is released from triglycerides after lipolysis directly enters the glycolysis pathway as dihydrooxyacetone phosphate (DHAP). Because one triglyceride molecule yields three fatty acid molecules with as much as 16 or more carbons in each one, fat molecules yield more energy than carbohydrates and are an

important source of energy for the human body. Triglycerides yield more than twice the energy per unit mass when compared to carbohydrates and proteins. Therefore, when glucose levels are low, triglycerides can be converted into acetyl CoA molecules and used to generate ATP through aerobic respiration.

Breakdown of Fatty Acids



During fatty acid oxidation, triglycerides can be broken down into acetyl CoA molecules and used for energy when glucose levels are low. In addition, excess acetyl CoA is converted to ketones via ketogenesis.

Ketogenesis

If excessive acetyl CoA is created from the oxidation of fatty acids and the Krebs cycle is overloaded and cannot handle it, the acetyl CoA is diverted to create **ketone bodies** (see [link]). These ketone bodies can serve as a fuel source if glucose levels are too low in the body. Ketones serve as fuel in times of prolonged starvation or when patients suffer from uncontrolled diabetes and cannot utilize most of the circulating glucose. In both cases, fat stores are liberated to generate energy through the Krebs cycle and will generate ketone bodies when too much acetyl CoA accumulates. However, ketones are acids which at high levels can cause the pH of the plasma to become acidic; a condition called ketoacidosis.

Ketone Body Oxidation

Organs that have classically been thought to be dependent solely on glucose, such as the brain, can actually use ketones as an alternative energy source. This keeps the brain functioning when glucose is limited. When ketones are produced faster than they can be used, they can be broken down into CO_2 and acetone. The acetone is removed by exhalation. One symptom of ketogenesis is that the patient's breath smells sweet like alcohol. This effect provides one way of telling if a diabetic is properly controlling the disease. The carbon dioxide produced can acidify the blood, leading to diabetic ketoacidosis, a dangerous condition in diabetics.

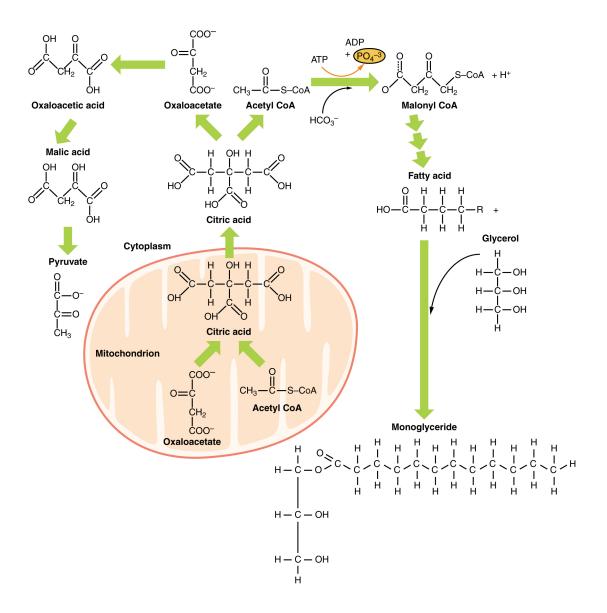
Lipogenesis

When glucose levels are plentiful, the excess acetyl CoA generated by glycolysis can be converted into fatty acids, triglycerides, cholesterol, steroids, and bile salts. This process, called **lipogenesis**, creates lipids (fat) from the acetyl CoA and takes place in the cytoplasm of adipocytes (fat cells) and hepatocytes (liver cells). When you eat more glucose or carbohydrates than your body needs, your system uses acetyl CoA to turn the excess into fat. Although there are several metabolic sources of acetyl CoA, it is most commonly derived from glycolysis. Acetyl CoA availability is significant, because it initiates lipogenesis. Lipogenesis begins with

acetyl CoA and advances by the subsequent addition of two carbon atoms from another acetyl CoA; this process is repeated until fatty acids are the appropriate length. Because this is a bond-creating anabolic process, ATP is consumed. However, the creation of triglycerides and lipids is an efficient way of storing the energy available in carbohydrates. Triglycerides and lipids, high-energy molecules, are stored in adipose tissue until they are needed.

Although lipogenesis occurs in the cytoplasm, the necessary acetyl CoA is created in the mitochondria and cannot be transported across the mitochondrial membrane. To solve this problem, pyruvate is converted into both oxaloacetate and acetyl CoA. Two different enzymes are required for these conversions. Oxaloacetate forms via the action of pyruvate carboxylase, whereas the action of pyruvate dehydrogenase creates acetyl CoA. Oxaloacetate and acetyl CoA combine to form citrate, which can cross the mitochondrial membrane and enter the cytoplasm. In the cytoplasm, citrate is converted back into oxaloacetate and acetyl CoA. Oxaloacetate is converted into malate and then into pyruvate. Pyruvate crosses back across the mitochondrial membrane to wait for the next cycle of lipogenesis. The acetyl CoA is converted into malonyl CoA that is used to synthesize fatty acids. [link] summarizes the pathways of lipid metabolism.

Lipid Metabolism



Lipids may follow one of several pathways during metabolism. Glycerol and fatty acids follow different pathways.

Chapter Review

Lipids are available to the body from three sources. They can be ingested in the diet, stored in the adipose tissue of the body, or synthesized in the liver. Fats ingested in the diet are digested in the small intestine. The triglycerides are broken down into monoglycerides and free fatty acids, then imported

across the intestinal mucosa. Once across, the triglycerides are resynthesized and transported to the liver or adipose tissue. Fatty acids are oxidized through fatty acid or β -oxidation into two-carbon acetyl CoA molecules, which can then enter the Krebs cycle to generate ATP. If excess acetyl CoA is created and overloads the capacity of the Krebs cycle, the acetyl CoA can be used to synthesize ketone bodies. When glucose is limited, ketone bodies can be oxidized and used for fuel. Excess acetyl CoA generated from excess glucose or carbohydrate ingestion can be used for fatty acid synthesis or lipogenesis. Acetyl CoA is used to create lipids, triglycerides, steroid hormones, cholesterol, and bile salts. Lipolysis is the breakdown of triglycerides into glycerol and fatty acids, making them easier for the body to process.

Glossary

beta (β)-oxidation fatty acid oxidation

bile salts

salts that are released from the liver in response to lipid ingestion and surround the insoluble triglycerides to aid in their conversion to monoglycerides and free fatty acids

cholecystokinin (CCK)

hormone that stimulates the release of pancreatic lipase and the contraction of the gallbladder to release bile salts

chylomicrons

vesicles containing cholesterol and triglycerides that transport lipids out of the intestinal cells and into the lymphatic and circulatory systems

fatty acid oxidation

breakdown of fatty acids into smaller chain fatty acids and acetyl CoA

ketone bodies

alternative source of energy when glucose is limited, created when too much acetyl CoA is created during fatty acid oxidation

lipogenesis

synthesis of lipids that occurs in the liver or adipose tissues

lipolysis

breakdown of triglycerides into glycerol and fatty acids

monoglyceride molecules

lipid consisting of a single fatty acid chain attached to a glycerol backbone

pancreatic lipases

enzymes released from the pancreas that digest lipids in the diet

triglycerides

lipids, or fats, consisting of three fatty acid chains attached to a glycerol backbone

OU Human Physiology: Protein Metabolism By the end of this section, you will be able to:

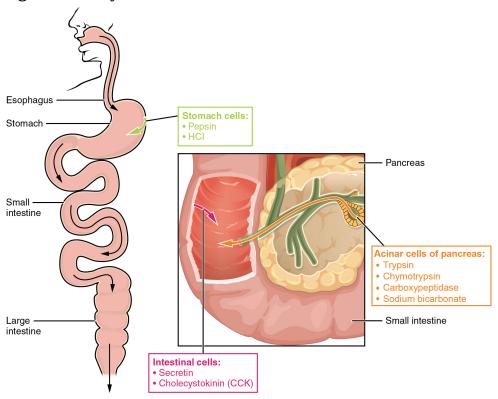
- Describe how the body digests proteins
- Explain how the urea cycle prevents toxic concentrations of nitrogen
- Differentiate between glucogenic and ketogenic amino acids
- Explain how protein can be used for energy

Much of the body is made of protein, and these proteins take on a myriad of forms. They represent cell signaling receptors, signaling molecules, structural members, enzymes, intracellular trafficking components, extracellular matrix scaffolds, ion pumps, ion channels, oxygen and CO₂ transporters (hemoglobin). That is not even the complete list! There is protein in bones (collagen), muscles, and tendons; the hemoglobin that transports oxygen; and enzymes that catalyze all biochemical reactions. Protein is also used for growth and repair. Amid all these necessary functions, proteins also hold the potential to serve as a metabolic fuel source. Proteins are not stored for later use, so excess proteins must be converted into glucose or triglycerides, and used to supply energy or build energy reserves. Although the body can synthesize proteins from amino acids, food is an important source of those amino acids, especially because humans cannot synthesize all of the 20 amino acids used to build proteins.

The digestion of proteins begins in the stomach. When protein-rich foods enter the stomach, they are greeted by a mixture of the enzyme **pepsin** and hydrochloric acid (HCl; 0.5 percent). The latter produces an environmental pH of 1.5–3.5 that denatures proteins within food. Pepsin cuts proteins into smaller polypeptides and their constituent amino acids. When the food-gastric juice mixture (chyme) enters the small intestine, the pancreas releases **sodium bicarbonate** to neutralize the HCl. This helps to protect the lining of the intestine. The small intestine also releases digestive hormones, including **secretin** and CCK, which stimulate digestive processes to break down the proteins further. Secretin also stimulates the pancreas to release sodium bicarbonate. The pancreas releases most of the digestive enzymes, including the proteases trypsin, chymotrypsin, and carboxypeptidase, which aid protein digestion. Together, all of these enzymes break complex proteins into smaller individual amino acids

([link]), which are then transported across the intestinal mucosa to be used to create new proteins, or to be converted into fats or acetyl CoA and used in the Krebs cycle.

Digestive Enzymes and Hormones



Enzymes in the stomach and small intestine break down proteins into amino acids. HCl in the stomach aids in proteolysis, and hormones secreted by intestinal cells direct the digestive processes.

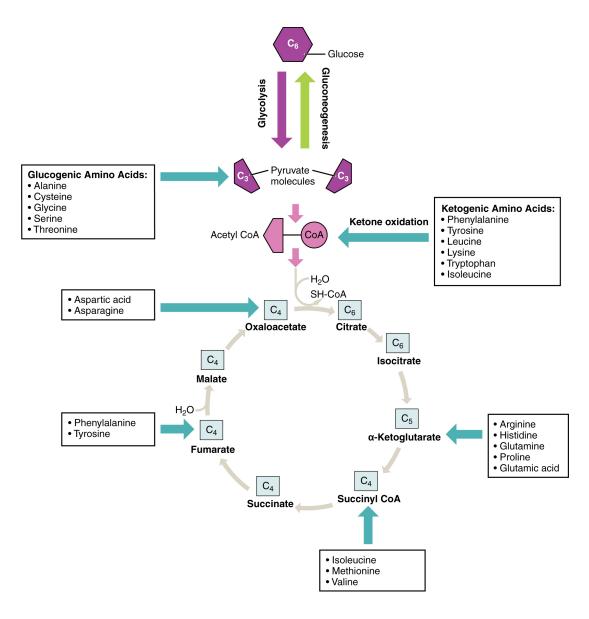
In order to avoid breaking down the proteins that make up the pancreas and small intestine, pancreatic enzymes are released as **inactive proenzymes** that are only activated in the small intestine. In the pancreas, vesicles store **trypsin**, **chymotrypsin**, and **procarboxypeptidase** as **trypsinogen**, **chymotrypsinogen**, and **carboxypeptidase**, respectively. Once released into the small intestine, an enzyme found in the wall of the small intestine, called **enterokinase**, binds to trypsinogen and converts it into its active form, trypsin. Trypsin then binds to chymotrypsinogen to convert it into the

active chymotrypsin. Trypsin and chymotrypsin break down large proteins into smaller peptides while carboxypeptidase cleaves individual amino acids, a process called **proteolysis**. These smaller peptides are catabolized into their constituent amino acids, which are transported across the apical surface of the intestinal mucosa in a process that is mediated by sodiumamino acid co-transporters. These transporters bind sodium and then bind the amino acid to transport it across the membrane. At the basal surface of the mucosal cells, the sodium and amino acid are released. The sodium can be reused in the transporter, whereas the amino acids are transferred into the bloodstream to be transported to the liver and cells throughout the body for protein synthesis.

Freely available amino acids are used to create proteins. If amino acids exist in excess, the body has no capacity or mechanism for their storage; thus, they are converted into glucose or ketones, or they are decomposed. Amino acid decomposition results in hydrocarbons and nitrogenous waste, which includes ammonia which is converted to urea in the liver via the urea cycle. This process produces a keto group that may be used in the Krebs cycle and hence is used as a source of energy.

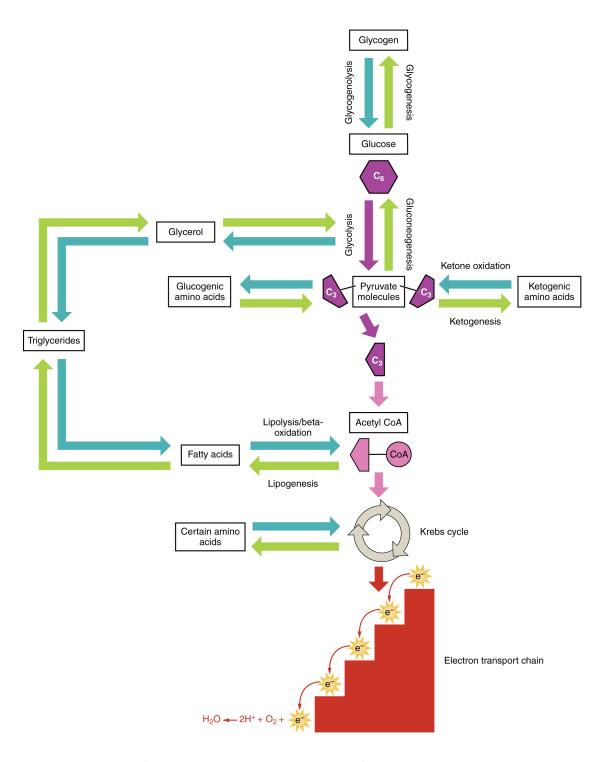
Amino acids can also be used as a source of energy, especially in times of starvation. Because the processing of amino acids results in the creation of metabolic intermediates, including pyruvate, acetyl CoA, acetoacyl CoA, oxaloacetate, and α -ketoglutarate, amino acids can serve as a source of energy production through the Krebs cycle ([link]). [link] summarizes the pathways of catabolism and anabolism for carbohydrates, lipids, and proteins.

Energy from Amino Acids



Amino acids can be broken down into precursors for glycolysis or the Krebs cycle. Amino acids (in bold) can enter the cycle through more than one pathway.

Catabolic and Anabolic Pathways



Nutrients follow a complex pathway from ingestion through anabolism and catabolism to energy production.

Note:

Disorders of the...

Metabolism: Pyruvate Dehydrogenase Complex Deficiency and Phenylketonuria

Pyruvate dehydrogenase complex deficiency (PDCD) and phenylketonuria (PKU) are genetic disorders. Pyruvate dehydrogenase is the enzyme that converts pyruvate into acetyl CoA, the molecule necessary to begin the Krebs cycle to produce ATP. With low levels of the pyruvate dehydrogenase complex (PDC), the rate of cycling through the Krebs cycle is dramatically reduced. This results in a decrease in the total amount of energy that is produced by the cells of the body. PDC deficiency results in a neurodegenerative disease that ranges in severity, depending on the levels of the PDC enzyme. It may cause developmental defects, muscle spasms, and death. Treatments can include diet modification, vitamin supplementation, and gene therapy; however, damage to the central nervous system usually cannot be reversed.

PKU affects about 1 in every 15,000 births in the United States. People afflicted with PKU lack sufficient activity of the enzyme phenylalanine hydroxylase and are therefore unable to break down phenylalanine into tyrosine adequately. Because of this, levels of phenylalanine rise to toxic levels in the body, which results in damage to the central nervous system and brain. Symptoms include delayed neurological development, hyperactivity, mental retardation, seizures, skin rash, tremors, and uncontrolled movements of the arms and legs. Pregnant women with PKU are at a high risk for exposing the fetus to too much phenylalanine, which can cross the placenta and affect fetal development. Babies exposed to excess phenylalanine in utero may present with heart defects, physical and/or mental retardation, and microcephaly. Every infant in the United States and Canada is tested at birth to determine whether PKU is present. The earlier a modified diet is begun, the less severe the symptoms will be. The person must closely follow a strict diet that is low in phenylalanine to avoid symptoms and damage. Phenylalanine is found in high concentrations in artificial sweeteners, including aspartame. Therefore, these sweeteners must be avoided. Some animal products and certain starches are also high in phenylalanine, and intake of these foods should be carefully monitored.

Chapter Review

Digestion of proteins begins in the stomach, where HCl and pepsin begin the process of breaking down proteins into their constituent amino acids. As the chyme enters the small intestine, it mixes with bicarbonate and digestive enzymes. The bicarbonate neutralizes the acidic HCl, and the digestive enzymes break down the proteins into smaller peptides and amino acids. Digestive hormones secretin and CCK are released from the small intestine to aid in digestive processes, and digestive proenzymes are released from the pancreas (trypsinogen and chymotrypsinogen). Enterokinase, an enzyme located in the wall of the small intestine, activates trypsin, which in turn activates chymotrypsin. These enzymes liberate the individual amino acids that are then transported via sodium-amino acid transporters across the intestinal wall into the cell. The amino acids are then transported into the bloodstream for dispersal to the liver and cells throughout the body to be used to create new proteins. When in excess, the amino acids are processed and stored as glucose or ketones. The nitrogen waste that is liberated in this process is converted to urea in the urea acid cycle and eliminated in the urine. In times of starvation, amino acids can be used as an energy source and processed through the Krebs cycle.

Glossary

carboxypeptidase pancreatic enzyme that digests protein

chymotrypsin pancreatic enzyme that digests protein

chymotrypsinogen proenzyme that is activated by trypsin into chymotrypsin

enterokinase

enzyme located in the wall of the small intestine that activates trypsin

inactive proenzymes

forms in which proteases are stored and released to prevent the inappropriate digestion of the native proteins of the stomach, pancreas, and small intestine

pepsin

enzyme that begins to break down proteins in the stomach

procarboxypeptidase

proenzyme that is activated by trypsin into carboxypeptidase

proteolysis

process of breaking proteins into smaller peptides

secretin

hormone released in the small intestine to aid in digestion

sodium bicarbonate

anion released into the small intestine to neutralize the pH of the food from the stomach

trypsin

pancreatic enzyme that activates chymotrypsin and digests protein

trypsinogen

proenzyme form of trypsin

OU Human Physiology: Metabolic States of the Body By the end of this section, you will be able to:

- Describe what defines each of the three metabolic states
- Describe the processes that occur during the absorptive state of metabolism
- Describe the processes that occur during the postabsorptive state of metabolism
- Explain how the body processes glucose when the body is starved of fuel

You eat periodically throughout the day; however, your organs, especially the brain, need a continuous supply of glucose. How does the body meet this constant demand for energy? Your body processes the food you eat both to use immediately and, importantly, to store as energy for later demands. If there were no method in place to store excess energy, you would need to eat constantly in order to meet energy demands. Distinct mechanisms are in place to facilitate energy storage, and to make stored energy available during times of fasting and starvation.

The Absorptive State

The **absorptive state**, or the fed state, occurs after a meal when your body is digesting the food and absorbing the nutrients (catabolism exceeds anabolism). Digestion begins the moment you put food into your mouth, as the food is broken down into its constituent parts to be absorbed through the intestine. The digestion of carbohydrates begins in the mouth, whereas the digestion of proteins and fats begins in the stomach and small intestine. The constituent parts of these carbohydrates, fats, and proteins are transported across the intestinal wall and enter the bloodstream (sugars and amino acids) or the lymphatic system (fats). From the intestines, these systems transport them to the liver, adipose tissue, or muscle cells that will process and use, or store, the energy.

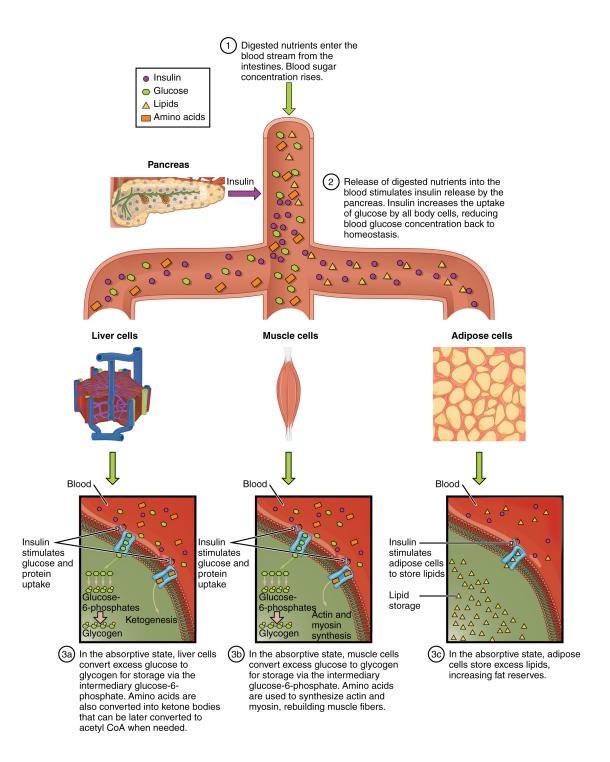
Depending on the amounts and types of nutrients ingested, the absorptive state can linger for up to 4 hours. The ingestion of food and the rise of glucose concentrations in the bloodstream stimulate pancreatic beta cells to

release **insulin** into the bloodstream, where it initiates the absorption of blood glucose by liver hepatocytes, and by adipose and muscle cells. Once inside these cells, glucose is immediately converted into glucose-6-phosphate. By doing this, a concentration gradient is established where glucose levels are higher in the blood than in the cells. This allows for glucose to continue moving from the blood to the cells where it is needed. Insulin also stimulates the storage of glucose as glycogen in the liver and muscle cells where it can be used for later energy needs of the body. Insulin also promotes the synthesis of protein in muscle. As you will see, muscle protein can be catabolized and used as fuel in times of starvation.

If energy is exerted shortly after eating, the dietary fats and sugars that were just ingested will be processed and used immediately for energy. If not, the excess glucose is stored as glycogen in the liver and muscle cells, or as fat in adipose tissue; excess dietary fat is also stored as triglycerides in adipose tissues.

[link] summarizes the metabolic processes occurring in the body during the absorptive state.

Absorptive State



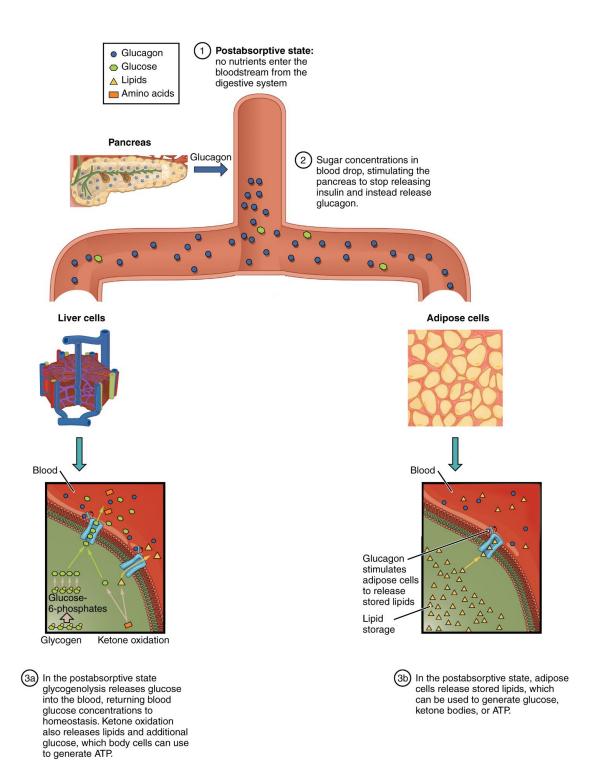
During the absorptive state, the body digests food and absorbs the nutrients.

The Postabsorptive State

The **postabsorptive state**, or the fasting state, occurs when the food has been digested, absorbed, and stored. You commonly fast overnight, but skipping meals during the day puts your body in the postabsorptive state as well. During this state, the body must rely initially on stored **glycogen**. Glucose levels in the blood begin to drop as it is absorbed and used by the cells. In response to the decrease in glucose, insulin levels also drop. Glycogen and triglyceride storage slows. However, due to the demands of the tissues and organs, blood glucose levels must be maintained in the normal range of 80–120 mg/dL. In response to a drop in blood glucose concentration, the hormone glucagon is released from the alpha cells of the pancreas. Glucagon acts upon the liver cells, where it inhibits the synthesis of glycogen and stimulates the breakdown of stored glycogen back into glucose. This glucose is released from the liver to be used by the peripheral tissues and the brain. As a result, blood glucose levels begin to rise. Gluconeogenesis will also begin in the liver to replace the glucose that has been used by the peripheral tissues.

After ingestion of food, fats and proteins are processed as described previously; however, the glucose processing changes a bit. The peripheral tissues preferentially absorb glucose. The liver, which normally absorbs and processes glucose, will not do so after a prolonged fast. The gluconeogenesis that has been ongoing in the liver will continue after fasting to replace the glycogen stores that were depleted in the liver. After these stores have been replenished, excess glucose that is absorbed by the liver will be converted into triglycerides and fatty acids for long-term storage. [link] summarizes the metabolic processes occurring in the body during the postabsorptive state.

Postabsorptive State



During the postabsorptive state, the body must rely on stored glycogen for energy.

Starvation

When the body is deprived of nourishment for an extended period of time, it goes into "survival mode." The first priority for survival is to provide enough glucose or fuel for the brain. The second priority is the conservation of amino acids for proteins. Therefore, the body uses ketones to satisfy the energy needs of the brain and other glucose-dependent organs, and to maintain proteins in the cells (see [link]). Because glucose levels are very low during starvation, glycolysis will shut off in cells that can use alternative fuels. For example, muscles will switch from using glucose to fatty acids as fuel. As previously explained, fatty acids can be converted into acetyl CoA and processed through the Krebs cycle to make ATP. Pyruvate, lactate, and alanine from muscle cells are not converted into acetyl CoA and used in the Krebs cycle, but are exported to the liver to be used in the synthesis of glucose. As starvation continues, and more glucose is needed, glycerol from fatty acids can be liberated and used as a source for gluconeogenesis.

After several days of starvation, ketone bodies become the major source of fuel for the heart and other organs. As starvation continues, fatty acids and triglyceride stores are used to create ketones for the body. This prevents the continued breakdown of proteins that serve as carbon sources for gluconeogenesis. Once these stores are fully depleted, proteins from muscles are released and broken down for glucose synthesis. Overall survival is dependent on the amount of fat and protein stored in the body.

Metabolic Rate

The **metabolic rate** is the amount of energy consumed minus the amount of energy expended by the body. The **basal metabolic rate (BMR)** describes the amount of daily energy expended by humans at rest, in a neutrally temperate environment, while in the postabsorptive state. It measures how much energy the body needs for normal, basic, daily activity. About 70 percent of all daily energy expenditure comes from the basic functions of the organs in the body. Another 20 percent comes from physical activity, and the remaining 10 percent is necessary for body thermoregulation or temperature control. This rate will be higher if a person is more active or

has more lean body mass. As you age, the BMR generally decreases as the percentage of less lean muscle mass decreases.

Chapter Review

There are three main metabolic states of the body: absorptive (fed), postabsorptive (fasting), and starvation. During any given day, your metabolism switches between absorptive and postabsorptive states. Starvation states happen very rarely in generally well-nourished individuals. When the body is fed, glucose, fats, and proteins are absorbed across the intestinal membrane and enter the bloodstream and lymphatic system to be used immediately for fuel. Any excess is stored for later fasting stages. As blood glucose levels rise, the pancreas releases insulin to stimulate the uptake of glucose by hepatocytes in the liver, muscle cells/fibers, and adipocytes (fat cells), and to promote its conversion to glycogen. As the postabsorptive state begins, glucose levels drop, and there is a corresponding drop in insulin levels. Falling glucose levels trigger the pancreas to release glucagon to turn off glycogen synthesis in the liver and stimulate its breakdown into glucose. The glucose is released into the bloodstream to serve as a fuel source for cells throughout the body. If glycogen stores are depleted during fasting, alternative sources, including fatty acids and proteins, can be metabolized and used as fuel. When the body once again enters the absorptive state after fasting, fats and proteins are digested and used to replenish fat and protein stores, whereas glucose is processed and used first to replenish the glycogen stores in the peripheral tissues, then in the liver. If the fast is not broken and starvation begins to set in, during the initial days, glucose produced from gluconeogenesis is still used by the brain and organs. After a few days, however, ketone bodies are created from fats and serve as the preferential fuel source for the heart and other organs, so that the brain can still use glucose. Once these stores are depleted, proteins will be catabolized first from the organs with fast turnover, such as the intestinal lining. Muscle will be spared to prevent the wasting of muscle tissue; however, these proteins will be used if alternative stores are not available.

Glossary

absorptive state

also called the fed state; the metabolic state occurring during the first few hours after ingesting food in which the body is digesting food and absorbing the nutrients

basal metabolic rate (BMR)

amount of energy expended by the body at rest

glycogen

form that glucose assumes when it is stored

insulin

hormone secreted by the pancreas that stimulates the uptake of glucose into the cells

metabolic rate

amount of energy consumed minus the amount of energy expended by the body

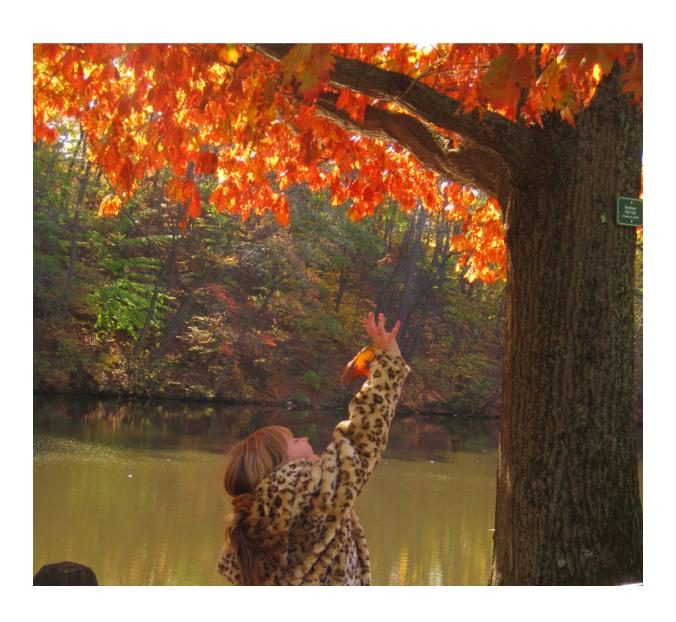
postabsorptive state

also called the fasting state; the metabolic state occurring after digestion when food is no longer the body's source of energy and it must rely on stored glycogen

OU Human Physiology: Endocrine Introduction class="introduction"

A Child Catches a Falling Leaf

Hormones of the endocrine system coordinate and control growth, metabolism, temperature regulation, the stress response, reproduction, and many other functions. (credit: "seenthroughmylense"/flickr.com)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Distinguish the types of intercellular communication, their importance, mechanisms, and effects.
- Identify the contributions of the endocrine system to homeostasis.
- Discuss the chemical composition of hormones and the mechanisms of hormone action.
- Discuss the site of production, regulation, and effects of the hormones of the pituitary, thyroid, parathyroid, adrenal, and pineal glands.
- Explain the role of the pancreatic endocrine cells in the regulation of blood glucose.
- Discuss several common diseases associated with endocrine system dysfunction.
- Identify the hormones released by the secondary endocrine organs.
- Discuss the embryonic development of and the effects of aging on, the endocrine system.

You may never have thought of it this way, but when you send a text message to two friends to meet you at the dining hall at six, you're sending digital signals that (you hope) will affect their behavior—even though they are some distance away. Similarly, certain cells send chemical signals to other cells in the body that influence their behavior. This long-distance intercellular communication, coordination, and control is critical for homeostasis, and it is the fundamental function of the endocrine system.

OU Human Physiology: An Overview of the Endocrine System By the end of this section, you will be able to:

- Distinguish the types of intercellular communication, their importance, mechanisms, and effects
- Identify the major organs and tissues of the endocrine system and their location in the body

Communication is a process in which a sender transmits signals to one or more receivers to control and coordinate actions. In the human body, two major organ systems participate heavily in communication: the nervous system and the endocrine system. Together, these two systems are primarily responsible for maintaining homeostasis in the body.

Neural and Endocrine Signaling

The nervous system uses two types of intercellular communication electrical and chemical signaling—either by the direct action of an electrical potential, or in the latter case, through the action of chemical neurotransmitters such as serotonin or norepinephrine. Neurotransmitters act locally and rapidly. When an electrical signal in the form of an action potential arrives at the synaptic terminal, they diffuse across the synaptic cleft (the gap between a sending neuron and a receiving neuron or muscle cell). Once the neurotransmitters interact (bind) with receptors on the receiving (post-synaptic) cell, the receptor stimulation is transduced into a response such as continued electrical signaling or modification of cellular response. The target cell responds within milliseconds of receiving the chemical "message"; this response then ceases very quickly once the neural signaling ends. In this way, neural communication enables body functions that involve quick, brief actions, such as movement, sensation, and cognition. In contrast, the **endocrine system** uses just one method of communication: chemical signaling. These signals are sent by the endocrine organs, which secrete chemicals—the **hormone**—into the extracellular fluid. Hormones are transported primarily via the bloodstream throughout the body, where they bind to receptors on target cells, inducing a characteristic response. As a result, endocrine signaling requires more time than neural signaling to prompt a response in target cells, though the precise amount of time varies with different hormones. For example, the hormones released when you are confronted with a dangerous or frightening situation, called the fight-or-flight response, occur by the release of adrenal hormones —epinephrine and norepinephrine—within seconds. In contrast, it may take up to 48 hours for target cells to respond to certain reproductive hormones.

Note:



Visit this <u>link</u> to watch an animation of the events that occur when a hormone binds to a cell membrane receptor. What is the secondary messenger made by adenylyl cyclase during the activation of liver cells by epinephrine?

In addition, endocrine signaling is typically less specific than neural signaling. The same hormone may play a role in a variety of different physiological processes depending on the target cells involved. For example, the hormone oxytocin promotes uterine contractions in women in labor. It is also important in breastfeeding, and may be involved in the sexual response and in feelings of emotional attachment in both males and females.

In general, the nervous system involves quick responses to rapid changes in the external environment, and the endocrine system is usually slower acting —taking care of the internal environment of the body, maintaining homeostasis, and controlling reproduction ([link]). So how does the fight-or-flight response that was mentioned earlier happen so quickly if hormones are usually slower acting? It is because the two systems are connected. It is the fast action of the nervous system in response to the danger in the

environment that stimulates the adrenal glands to secrete their hormones. As a result, the nervous system can cause rapid endocrine responses to keep up with sudden changes in both the external and internal environments when necessary.

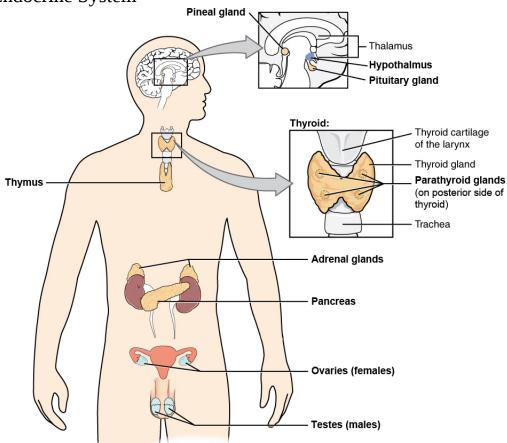
Endocrine and Nervous Systems			
	Endocrine system	Nervous system	
Signaling mechanism(s)	Chemical	Chemical/electrical	
Primary chemical signal	Hormones	Neurotransmitters	
Distance traveled	Long or short	Always short	
Response time	Fast or slow	Always fast	
Environment targeted	Internal	Internal and external	

Structures of the Endocrine System

The endocrine system consists of cells, tissues, and organs that secrete hormones as a primary or secondary function. The **endocrine gland** is the major player in this system. The primary function of these ductless glands is to secrete their hormones directly into the surrounding fluid. The interstitial fluid and the blood vessels then transport the hormones throughout the body. The endocrine system includes the pituitary, thyroid, parathyroid,

adrenal, and pineal glands ([link]). Other organs that play a role in the endocrine have non-endocrine functions as well. For example, the pancreas contains cells that function in digestion as well as cells that secrete the hormones insulin and glucagon, which regulate blood glucose levels. The hypothalamus, thymus, heart, kidneys, stomach, small intestine, liver, skin, female ovaries, and male testes are other organs that contain cells with endocrine function. Moreover, adipose tissue has long been known to produce hormones, and recent research has revealed that even bone tissue has endocrine functions.

Endocrine System



Endocrine glands and cells are located throughout the body and play an important role in homeostasis. Organ names in bold are considered primary endocrine organs since their major role is to synthesize and secrete hormones. The ductless endocrine glands are not to be confused with the body's **exocrine system**, whose glands release their secretions through ducts. Examples of exocrine glands include the sebaceous and sweat glands of the skin. As just noted, the pancreas also has an exocrine function: most of its cells secrete pancreatic juice through the pancreatic and accessory ducts to the lumen of the small intestine.

Other Types of Chemical Signaling

In endocrine signaling, hormones secreted into the extracellular fluid diffuse into the blood or lymph, and can then travel great distances throughout the body. In contrast, autocrine signaling takes place within the same cell. An **autocrine** (auto- = "self") is a chemical that elicits a response in the same cell that secreted it. Interleukin-1, or IL-1, is a signaling molecule that plays an important role in inflammatory response. The cells that secrete IL-1 have receptors on their cell surface that bind these molecules, resulting in autocrine signaling.

Local intercellular communication is the province of the **paracrine**, also called a paracrine factor, which is a chemical that induces a response in neighboring cells. Although paracrines may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues. A familiar example to those with asthma is histamine, a paracrine that is released by immune cells in the bronchial tree. Histamine causes the smooth muscle cells of the bronchi to constrict, narrowing the airways.

Note:

Career Connections

Endocrinologist

Endocrinology is a specialty in the field of medicine that focuses on the treatment of endocrine system disorders. Endocrinologists—medical doctors who specialize in this field—are experts in treating diseases associated with hormonal systems, ranging from thyroid disease to diabetes mellitus. Endocrine surgeons treat endocrine disease through the removal, or resection, of the affected endocrine gland.

Patients who are referred to endocrinologists may have signs and symptoms or blood test results that suggest excessive or impaired functioning of an endocrine gland or endocrine cells. The endocrinologist may order additional blood tests to determine whether the patient's hormonal levels are abnormal, or they may stimulate or suppress the function of the suspect endocrine gland and then have blood taken for analysis. Treatment varies according to the diagnosis. Some endocrine disorders, such as type 2 diabetes, may respond to lifestyle changes such as modest weight loss, adoption of a healthy diet, and regular physical activity. Other disorders may require medication, such as hormone replacement, and routine monitoring by the endocrinologist. These include disorders of the pituitary gland that can affect growth and disorders of the thyroid gland that can result in a variety of metabolic problems. Some patients experience health problems as a result of the normal decline in hormones that can accompany aging. These patients can consult with an endocrinologist to weigh the risks and benefits of hormone replacement therapy intended to boost their natural levels of reproductive hormones. In addition to treating patients, endocrinologists may be involved in research to improve the understanding of endocrine system disorders and develop new treatments for these diseases.

Chapter Review

The endocrine system consists of cells, tissues, and organs that secrete hormones critical to homeostasis. The body coordinates its functions through two major types of communication: neural and endocrine. Neural communication includes both electrical and chemical signaling between neurons and target cells. Endocrine communication involves chemical signaling via the release of hormones into the extracellular fluid. From there, hormones diffuse into the bloodstream and may travel to distant body regions, where they elicit a response in target cells. Endocrine glands are ductless glands that secrete hormones. Many organs of the body with other primary functions—such as the heart, stomach, and kidneys—also have hormone-secreting cells.

Glossary

autocrine

chemical signal that elicits a response in the same cell that secreted it

endocrine gland

tissue or organ that secretes hormones into the blood and lymph without ducts such that they may be transported to organs distant from the site of secretion

endocrine system

cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes

exocrine system

cells, tissues, and organs that secrete substances directly to target tissues via glandular ducts

hormone

secretion of an endocrine organ that travels via the bloodstream or lymphatics to induce a response in target cells or tissues in another part of the body

paracrine

chemical signal that elicits a response in neighboring cells; also called paracrine factor

OU Human Physiology: Hormones By the end of this section, you will be able to:

- Identify the three major classes of hormones on the basis of chemical structure
- Compare and contrast intracellular and cell membrane hormone receptors
- Describe signaling pathways that involve cAMP and IP3
- Identify several factors that influence a target cell's response
- Discuss the role of feedback loops and humoral, hormonal, and neural stimuli in hormone control
- Based on their chemical structure explain how they are synthesized and secreted by the secretory cell, how they are transported to their target, the location of receptor binding, and the general target cell response

Although a given hormone may travel throughout the body in the bloodstream, it will affect the activity only of its target cells; that is, cells with receptors for that particular hormone. Once the hormone binds to the receptor, a chain of events is initiated that leads to the target cell's response. Hormones play a critical role in the regulation of physiological processes because of the target cell responses they regulate. These responses contribute to human reproduction, growth and development of body tissues, metabolism, fluid, and electrolyte balance, sleep, and many other body functions. The major hormones of the human body and their effects are identified in [link].

Endocrine Glands and Their Major Hormones			
Endocrine gland	Associated hormones	Chemical class	Effect
Pituitary (anterior)	Growth hormone (GH)	Protein	Promotes growth of body tissues

Endocrine Glands and Their Major Hormones			
Endocrine gland	Associated hormones	Chemical class	Effect
Pituitary (anterior)	Prolactin (PRL)	Peptide	Promotes milk production
Pituitary (anterior)	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release
Pituitary (anterior)	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Pituitary (anterior)	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production
Pituitary (anterior)	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads
Pituitary (posterior)	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys
Pituitary (posterior)	Oxytocin	Peptide	Stimulates uterine contractions during childbirth

Endocrine Glands and Their Major Hormones			
Endocrine gland	Associated hormones	Chemical class	Effect
Thyroid	Thyroxine (T_4) , triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate
Thyroid	Calcitonin	Peptide	Reduces blood Ca ²⁺ levels
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increases blood Ca ²⁺ levels
Adrenal (cortex)	Aldosterone	Steroid	Increases blood Na ⁺ levels
Adrenal (cortex)	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal (medulla)	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response
Pineal	Melatonin	Amine	Regulates sleep cycles
Pancreas	Insulin	Protein	Reduces blood glucose levels

Endocrine Glands and Their Major Hormones			
Endocrine gland	Associated hormones	Chemical class	Effect
Pancreas	Glucagon	Protein	Increases blood glucose levels
Testes	Testosterone	Steroid	Stimulates development of male secondary sex characteristics and sperm production
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of female secondary sex characteristics and prepare the body for childbirth

Types of Hormones

The hormones of the human body can be divided into two major groups on the basis of their chemical structure. Hormones derived from amino acids include amines, peptides, and proteins. Those derived from lipids include steroids ([link]). These chemical groups affect a hormone's distribution, the type of receptors it binds to, and other aspects of its function.

Amine, Peptide, Protein, and Steroid Hormone Structure

Hormone Class	Components	Example(s)	
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	Norepinephrine OH NH ₂ OH OH	
Peptide/Protein Hormones	Peptide: Short chains of linked amino acids	Oxytocin Gly Leu Pro Cys Asp Glu Tyr Ile	
	Protein: long chains of linked amino acids	Growth Hormone	
Steroid Hormones	Derived from the lipid cholesterol	Testosterone Progesterone CH ₃ C = O H ₃ C H ₃ C H ₃ C C = O	

Amine Hormones

Hormones derived from the modification of amino acids are referred to as amine hormones. Typically, the original structure of the amino acid is modified such that a -COOH, or carboxyl, group is removed, whereas the $-\text{NH}_3^+$, or amine, group remains.

Amine hormones are synthesized from the amino acids tryptophan or tyrosine. An example of a hormone derived from tryptophan is melatonin, which is secreted by the pineal gland and helps regulate circadian rhythm. Tyrosine derivatives include the metabolism-regulating thyroid hormones, as well as the catecholamines, such as epinephrine, norepinephrine, and dopamine. Epinephrine and norepinephrine are secreted by the adrenal medulla and play a role in the fight-or-flight response, whereas dopamine is secreted by the hypothalamus and inhibits the release of certain anterior pituitary hormones.

Peptide and Protein Hormones

Whereas the amine hormones are derived from a single amino acid, peptide and protein hormones consist of multiple amino acids that link to form an amino acid chain. Peptide hormones consist of short chains of amino acids, whereas protein hormones are longer polypeptides. Both types are synthesized like other body proteins: DNA is transcribed into mRNA, which is translated into an amino acid chain.

Examples of peptide hormones include antidiuretic hormone (ADH), a pituitary hormone important in fluid balance, and atrial-natriuretic peptide, which is produced by the heart and helps to decrease blood pressure. Some examples of protein hormones include growth hormone, which is produced by the pituitary gland, and follicle-stimulating hormone (FSH), which has an attached carbohydrate group and is thus classified as a glycoprotein. FSH helps stimulate the maturation of eggs in the ovaries and sperm in the testes.

Steroid Hormones

The primary hormones derived from lipids are steroids. Steroid hormones are derived from the lipid cholesterol. For example, the reproductive hormones testosterone and the estrogens—which are produced by the gonads (testes and ovaries)—are steroid hormones. The adrenal glands produce the steroid hormone aldosterone, which is involved in osmoregulation, and cortisol, which plays a role in metabolism.

Like cholesterol, steroid hormones are not soluble in water (they are hydrophobic). Because blood is water-based, lipid-derived hormones must travel

to their target cell bound to a transport protein. This more complex structure extends the half-life of steroid hormones much longer than that of hormones derived from amino acids. A hormone's half-life is the time required for half the concentration of the hormone to be degraded. For example, the lipid-derived hormone cortisol has a half-life of approximately 60 to 90 minutes. In contrast, the amino acid—derived hormone epinephrine has a half-life of approximately one minute.

Pathways of Hormone Action

The message a hormone sends is received by a **hormone receptor**, a protein located either inside the cell or within the cell membrane. The receptor will process the message by initiating other signaling events or cellular mechanisms that result in the target cell's response. Hormone receptors recognize molecules with specific shapes and side groups, and respond only to those hormones that are recognized. The same type of receptor may be located on cells in different body tissues, and trigger somewhat different responses. Thus, the response triggered by a hormone depends not only on the hormone, but also on the target cell.

Once the target cell receives the hormone signal, it can respond in a variety of ways. The response may include the stimulation of protein synthesis, activation or deactivation of enzymes, alteration in the permeability of the cell membrane, altered rates of mitosis and cell growth, and stimulation of the secretion of products. Moreover, a single hormone may be capable of inducing different responses in a given cell.

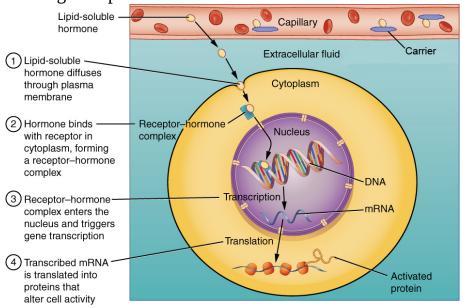
Pathways Involving Intracellular Hormone Receptors

Intracellular hormone receptors are located inside the cell. Hormones that bind to this type of receptor must be able to cross the cell membrane. Steroid hormones are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor ([link]). Thyroid hormones, which contain benzene rings studded with iodine, are also lipid-soluble and can enter the cell.

The location of steroid and thyroid hormone binding differs slightly: a steroid hormone may bind to its receptor within the cytosol or within the nucleus. In

either case, this binding generates a hormone-receptor complex that moves toward the chromatin in the cell nucleus and binds to a particular segment of the cell's DNA. In contrast, thyroid hormones bind to receptors already bound to DNA. For both steroid and thyroid hormones, binding of the hormone-receptor complex with DNA triggers transcription of a target gene to mRNA, which moves to the cytosol and directs protein synthesis by ribosomes.

Binding of Lipid-Soluble Hormones

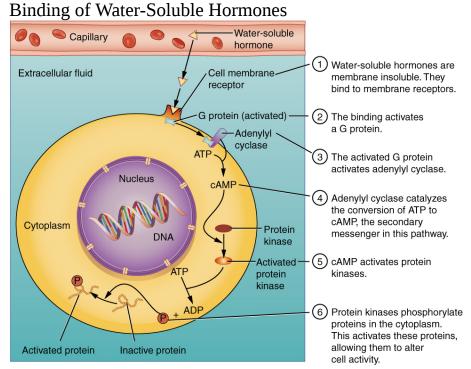


A steroid hormone directly initiates the production of proteins within a target cell. Steroid hormones easily diffuse through the cell membrane. The hormone binds to its receptor in the cytosol, forming a receptor—hormone complex. The receptor—hormone complex then enters the nucleus and binds to the target gene on the DNA. Transcription of the gene creates a messenger RNA that is translated into the desired protein within the cytoplasm.

Pathways Involving Cell Membrane Hormone Receptors

Hydrophilic, or water-soluble, hormones are unable to diffuse through the lipid bilayer of the cell membrane and must therefore pass on their message to a receptor located at the surface of the cell. Except for thyroid hormones, which are lipid-soluble, all amino acid—derived hormones bind to cell membrane receptors that are located, at least in part, on the extracellular surface of the cell membrane. Therefore, they do not directly affect the transcription of target genes, but instead initiate a signaling cascade that is carried out by a molecule called a **second messenger**. In this case, the hormone is called a **first messenger**.

The second messenger used by most hormones is **cyclic adenosine monophosphate (cAMP)**. In the cAMP second messenger system, a watersoluble hormone binds to its receptor in the cell membrane (Step 1 in [link]). This receptor is associated with an intracellular component called a **G protein**, and binding of the hormone activates the G-protein component (Step 2). The activated G protein in turn activates an enzyme called **adenylate cyclase**, also known as adenylyl cyclase (Step 3), which converts adenosine triphosphate (ATP) to cAMP (Step 4). As the second messenger, cAMP activates a type of enzyme called a **protein kinase** that is present in the cytosol (Step 5). Activated protein kinases initiate a **phosphorylation cascade**, in which multiple protein kinases phosphorylate (add a phosphate group to) numerous and various cellular proteins, including other enzymes (Step 6).



Water-soluble hormones cannot diffuse through the

cell membrane. These hormones must bind to a surface cell-membrane receptor. The receptor then initiates a cell-signaling pathway within the cell involving G proteins, adenylate cyclase, the secondary messenger cyclic AMP (cAMP), and protein kinases. In the final step, these protein kinases phosphorylate proteins in the cytoplasm. This activates proteins in the cell that carry out the changes specified by the hormone.

The phosphorylation of cellular proteins can trigger a wide variety of effects, from nutrient metabolism to the synthesis of different hormones and other products. The effects vary according to the type of target cell, the G proteins and kinases involved, and the phosphorylation of proteins. Examples of hormones that use cAMP as a second messenger include calcitonin, which is important for bone construction and regulating blood calcium levels; glucagon, which plays a role in blood glucose levels; and thyroid-stimulating hormone, which causes the release of T_3 and T_4 from the thyroid gland.

Overall, the phosphorylation cascade significantly increases the efficiency, speed, and specificity of the hormonal response, as thousands of signaling events can be initiated simultaneously in response to a very low concentration of hormone in the bloodstream. However, the duration of the hormone signal is short, as cAMP is quickly deactivated by the enzyme **phosphodiesterase** (**PDE**), which is located in the cytosol. The action of PDE helps to ensure that a target cell's response ceases quickly unless new hormones arrive at the cell membrane. To further ensure the response ceases quickly an enzyme called phosphatase will dephosphorylate the protein, the G-protein will be hydrolyzed and returned to its original configuration and the ligand will no longer be bound to the receptor and will soon be degraded.

Importantly, there are also G proteins that decrease the levels of cAMP in the cell in response to hormone binding. When growth hormone—inhibiting hormone (GHIH), also known as somatostatin, binds to its receptors in the pituitary gland, for example, the level of cAMP decreases, thereby inhibiting the secretion of human growth hormone.

Not all water-soluble hormones initiate the cAMP second messenger system. One common alternative system uses calcium ions as a second messenger. In this system, G proteins activate the enzyme phospholipase C (PLC), which functions similarly to adenylyl cyclase. Once activated, PLC cleaves a membrane-bound phospholipid into two molecules: diacylglycerol (DAG) and inositol triphosphate (IP₃). Like cAMP, DAG activates protein kinases that initiate a phosphorylation cascade. At the same time, IP₃ causes calcium ions to be released from storage sites within the cytosol, such as from within the smooth endoplasmic reticulum. The calcium ions then act as second messengers in two ways: they can influence enzymatic and other cellular activities directly, or they can bind to calcium-binding proteins, the most common of which is calmodulin. Upon binding calcium, calmodulin is able to modulate protein kinase within the cell. Examples of hormones that use calcium ions as a second messenger system include angiotensin II, which helps regulate blood pressure through vasoconstriction, and growth hormone–releasing hormone (GHRH), which causes the pituitary gland to release growth hormones.

Factors Affecting Target Cell Response

You will recall that target cells must have receptors specific to a given hormone if that hormone is to trigger a response. But several other factors influence the target cell response. For example, the presence of a significant level of a hormone circulating in the bloodstream can cause its target cells to decrease their number of receptors for that hormone. This process is called **downregulation**, and it allows cells to become less reactive to the excessive hormone levels. When the level of a hormone is chronically reduced, target cells engage in **upregulation** to increase their number of receptors. This process allows cells to be more sensitive to the hormone that is present. Cells can also alter the sensitivity of the receptors themselves to various hormones.

Two or more hormones can interact to affect the response of cells in a variety of ways. The three most common types of interaction are as follows:

• The permissive effect, in which the presence of one hormone enables another hormone to act. For example, thyroid hormones have complex permissive relationships with certain reproductive hormones. A dietary deficiency of iodine, a component of thyroid hormones, can therefore affect reproductive system development and functioning.

- The synergistic effect, in which two hormones with similar effects produce an amplified response. In some cases, two hormones are required for an adequate response. For example, two different reproductive hormones—FSH from the pituitary gland and estrogens from the ovaries—are required for the maturation of female ova (egg cells).
- The antagonistic effect, in which two hormones have opposing effects. A familiar example is the effect of two pancreatic hormones, insulin and glucagon. Insulin increases the liver's storage of glucose as glycogen, decreasing blood glucose, whereas glucagon stimulates the breakdown of glycogen stores, increasing blood glucose.

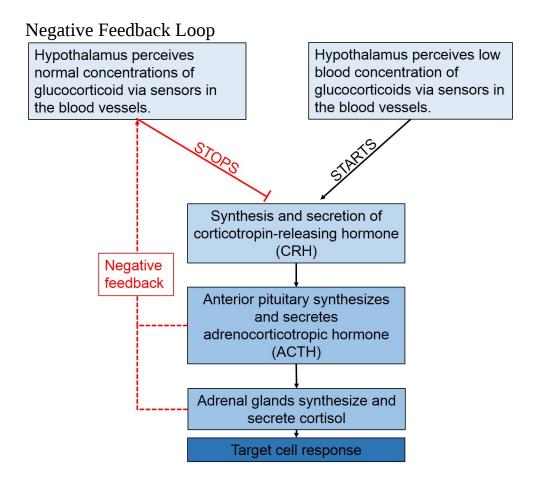
Regulation of Hormone Secretion

To prevent abnormal hormone levels and a potential disease state, hormone levels must be tightly controlled. The body maintains this control by balancing hormone production and degradation. Feedback loops govern the initiation and maintenance of most hormone secretion in response to various stimuli.

Role of Feedback Loops

The contribution of feedback loops to homeostasis will only be briefly reviewed here. Positive feedback loops are characterized by the release of additional hormone in response to an original hormone release. The release of oxytocin during childbirth is a positive feedback loop. The initial release of oxytocin begins to signal the uterine muscles to contract, which pushes the fetus toward the cervix, causing it to stretch. This, in turn, signals the pituitary gland to release more oxytocin, causing labor contractions to intensify. The release of oxytocin decreases after the birth of the child.

The more common method of hormone regulation is the negative feedback loop. Negative feedback is characterized by the inhibition of further secretion of a hormone in response to adequate levels of that hormone. This allows blood levels of the hormone to be regulated within a narrow range. An example of a negative feedback loop is the release of glucocorticoid hormones from the adrenal glands, as directed by the hypothalamus and pituitary gland. As glucocorticoid concentrations in the blood rise, the hypothalamus and pituitary gland reduce their signaling to the adrenal glands to prevent additional glucocorticoid secretion ([link]).



The release of adrenal glucocorticoids (i.e. cortisol) is stimulated by the release of hormones from the hypothalamus and pituitary gland. This signaling is inhibited when glucocorticoid levels become elevated by causing negative signals to the pituitary gland and hypothalamus.

Role of Endocrine Gland Stimuli

Reflexes triggered by both chemical and neural stimuli control endocrine activity. These reflexes may be simple, involving only one hormone response, or they may be more complex and involve many hormones, as is the case with the hypothalamic control of various anterior pituitary—controlled hormones.

Humoral stimuli are changes in blood levels of non-hormone chemicals, such as nutrients or ions, which cause the release or inhibition of a hormone to, in turn, maintain homeostasis. For example, osmoreceptors in the hypothalamus detect changes in blood osmolarity (the concentration of solutes in the blood plasma). If blood osmolarity is too high, meaning that the blood is not dilute enough, osmoreceptors signal the hypothalamus to release ADH. The hormone causes the kidneys to reabsorb more water and reduce the volume of urine produced. This reabsorption causes a reduction of the osmolarity of the blood, diluting the blood to the appropriate level. The regulation of blood glucose is another example. High blood glucose levels cause the release of insulin from the pancreas, which increases glucose uptake by cells and liver storage of glucose as glycogen.

An endocrine gland may also secrete a hormone in response to the presence of another hormone produced by a different endocrine gland. Such hormonal stimuli often involve the hypothalamus, which produces releasing and inhibiting hormones that control the secretion of a variety of pituitary hormones.

In addition to these chemical signals, hormones can also be released in response to neural stimuli. A common example of neural stimuli is the activation of the fight-or-flight response by the sympathetic nervous system. When an individual perceives danger, sympathetic neurons signal the adrenal glands to secrete norepinephrine and epinephrine. The two hormones dilate blood vessels, increase the heart and respiratory rate, and suppress the digestive and immune systems. These responses boost the body's transport of oxygen to the brain and muscles, thereby improving the body's ability to fight or flee.

Note:

Everyday Connections

Bisphenol A and Endocrine Disruption

You may have heard news reports about the effects of a chemical called bisphenol A (BPA) in various types of food packaging. BPA is used in the manufacturing of hard plastics and epoxy resins. Common food-related items that may contain BPA include the lining of aluminum cans, plastic food-storage containers, drinking cups, as well as baby bottles and "sippy" cups. Other uses of BPA include medical equipment, dental fillings, and the lining of water pipes.

Research suggests that BPA is an endocrine disruptor, meaning that it negatively interferes with the endocrine system, particularly during the prenatal and postnatal development period. In particular, BPA mimics the hormonal effects of estrogens and has the opposite effect—that of androgens. The U.S. Food and Drug Administration (FDA) notes in their statement about BPA safety that although traditional toxicology studies have supported the safety of low levels of exposure to BPA, recent studies using novel approaches to test for subtle effects have led to some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. The FDA is currently facilitating decreased use of BPA in food-related materials. Many US companies have voluntarily removed BPA from baby bottles, "sippy" cups, and the linings of infant formula cans, and most plastic reusable water bottles sold today boast that they are "BPA free." In contrast, both Canada and the European Union have completely banned the use of BPA in baby products.

The potential harmful effects of BPA have been studied in both animal models and humans and include a large variety of health effects, such as developmental delay and disease. For example, prenatal exposure to BPA during the first trimester of human pregnancy may be associated with wheezing and aggressive behavior during childhood. Adults exposed to high levels of BPA may experience altered thyroid signaling and male sexual dysfunction. BPA exposure during the prenatal or postnatal period of development in animal models has been observed to cause neurological delays, changes in brain structure and function, sexual dysfunction, asthma, and increased risk for multiple cancers. In vitro studies have also shown that BPA exposure causes molecular changes that initiate the development of cancers of the breast, prostate, and brain. Although these studies have implicated BPA in numerous ill health effects, some experts caution that some of these studies may be flawed and that more research needs to be done. In the meantime, the FDA recommends that consumers take precautions to limit their exposure to BPA. In addition to purchasing foods in packaging free of BPA, consumers should avoid carrying or storing foods or liquids in bottles with the recycling code 3 or 7. Foods and liquids should not be microwave-heated in any form of plastic: use paper, glass, or ceramics instead.

Chapter Review

Hormones are derived from amino acids or lipids. Amine hormones originate from the amino acids tryptophan or tyrosine. Larger amino acid hormones include peptides and protein hormones. Steroid hormones are derived from cholesterol.

Steroid hormones and thyroid hormone are lipid soluble. All other amino acid—derived hormones are water soluble. Hydrophobic hormones are able to diffuse through the membrane and interact with an intracellular receptor. In contrast, hydrophilic hormones must interact with cell membrane receptors. These are typically associated with a G protein, which becomes activated when the hormone binds the receptor. This initiates a signaling cascade that involves a second messenger, such as cyclic adenosine monophosphate (cAMP). Second messenger systems greatly amplify the hormone signal, creating a broader, more efficient, and faster response.

Hormones are released upon stimulation that is of either chemical or neural origin. Regulation of hormone release is primarily achieved through negative feedback. Various stimuli may cause the release of hormones, but there are three major types. Humoral stimuli are changes in ion or nutrient levels in the blood. Hormonal stimuli are changes in hormone levels that initiate or inhibit the secretion of another hormone. Finally, a neural stimulus occurs when a nerve impulse prompts the secretion or inhibition of a hormone.

Glossary

adenylate cyclase

membrane-bound enzyme that converts ATP to cyclic AMP, creating cAMP, as a result of G-protein activation

cyclic adenosine monophosphate (cAMP)

second messenger that, in response to adenylyl cyclase activation, triggers a phosphorylation cascade

diacylglycerol (DAG)

molecule that, like cAMP, activates protein kinases, thereby initiating a phosphorylation cascade

downregulation

decrease in the number of hormone receptors, typically in response to chronically excessive levels of a hormone

first messenger

hormone that binds to a cell membrane hormone receptor and triggers activation of a second messenger system

G protein

protein associated with a cell membrane hormone receptor that initiates the next step in a second messenger system upon activation by hormone—receptor binding

hormone receptor

protein within a cell or on the cell membrane that binds a hormone, initiating the target cell response

inositol triphosphate (IP₃)

molecule that initiates the release of calcium ions from intracellular stores

phosphodiesterase (PDE)

cytosolic enzyme that deactivates and degrades cAMP

phosphorylation cascade

signaling event in which multiple protein kinases phosphorylate the next protein substrate by transferring a phosphate group from ATP to the protein

protein kinase

enzyme that initiates a phosphorylation cascade upon activation

second messenger

molecule that initiates a signaling cascade in response to hormone binding on a cell membrane receptor and activation of a G protein

upregulation

increase in the number of hormone receptors, typically in response to chronically reduced levels of a hormone

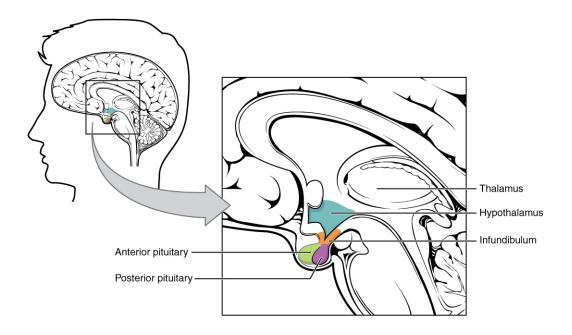
OU Human Physiology: The Pituitary Gland and Hypothalamus By the end of this section, you will be able to:

- Explain the interrelationships of the anatomy and functions of the hypothalamus and the posterior and anterior lobes of the pituitary gland
- Identify the two hormones released from the posterior pituitary, their target cells, and their principal actions
- Explain how oxytocin and antidiuretic are synthesized and secreted from the hypothalamus and where they are stored until needed by the body
- Identify the six hormones produced by the anterior pituitary, their target cells, their principal actions, and their regulation by the hypothalamus
- Describe feedback loops for the six hormones produced by the anterior pituitary
- List the chemical class for the hormones of the anterior pituitary and posterior pituitary

The hypothalamus—pituitary complex can be thought of as the "command center" of the endocrine system. This complex secretes several hormones that directly produce responses in target tissues, as well as hormones that regulate the synthesis and secretion of hormones of other glands. In addition, the hypothalamus—pituitary complex coordinates the messages of the endocrine and nervous systems. In many cases, a stimulus received by the nervous system must pass through the hypothalamus—pituitary complex to be translated into hormones that can initiate a response.

The **hypothalamus** is a structure of the diencephalon of the brain located anterior and inferior to the thalamus ([link]). It has both neural and endocrine functions, producing and secreting many hormones. In addition, the hypothalamus is anatomically and functionally related to the **pituitary gland** (or hypophysis), a bean-sized organ suspended from it by a stem called the **infundibulum** (or pituitary stalk). The pituitary gland consists of two lobes that arise from distinct parts of embryonic tissue: the posterior pituitary (neurohypophysis) is neural tissue, whereas the anterior pituitary (also known as the adenohypophysis) is glandular tissue that develops from the primitive digestive tract. The hormones secreted by the posterior and anterior pituitary are summarized in [link].

Hypothalamus–Pituitary Complex



The hypothalamus region lies inferior and anterior to the thalamus. It connects to the pituitary gland by the stalk-like infundibulum. The pituitary gland consists of an anterior and posterior lobe, with each lobe secreting different hormones in response to signals from the hypothalamus.

Pituitary H	ituitary Hormones			
Pituitary lobe	Associated hormones	Chemical class	Effect	
Anterior	Growth hormone (GH)	Protein	Promotes growth of body tissues	

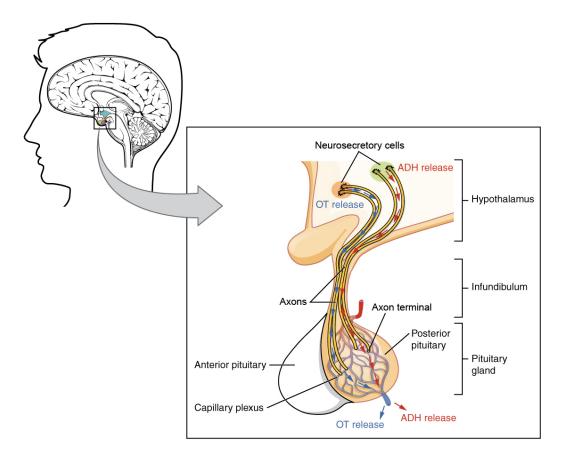
Pituitary H	ituitary Hormones				
Pituitary lobe	Associated hormones	Chemical class	Effect		
Anterior	Prolactin (PRL)	Peptide	Promotes milk production from mammary glands		
Anterior	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release from thyroid		
Anterior	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex		
Anterior	Follicle-stimulating hormone (FSH)	- (TIV(CODIC)(PIII			
Anterior	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads		

Pituitary H	ituitary Hormones			
Pituitary lobe	Associated hormones	Chemical class	Effect	
Posterior	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys	
Posterior	Oxytocin	Peptide	Stimulates uterine contractions during childbirth	

Posterior Pituitary

The posterior pituitary is actually an extension of the neurons of the paraventricular and supraoptic nuclei of the hypothalamus. The cell bodies of these neurons rest in the hypothalamus, but their axons descend within the infundibulum, and end in axon terminals that comprise the posterior pituitary ([link]).

Posterior Pituitary



Neurosecretory cells in the hypothalamus release oxytocin (OT) or ADH into the posterior lobe of the pituitary gland. These hormones are stored in the posterior pituitary and when needed are released into the blood via the capillary plexus.

The posterior pituitary gland does not produce hormones, but rather stores and secretes hormones produced by the hypothalamus. Both the paraventricular nuclei and supraoptic nuclie produce oxytocin and antidiuretic hormone (ADH). These hormones travel along the axons into storage sites in the axon terminals of the posterior pituitary. In response to signals from the same hypothalamic neurons, the hormones are released from the axon terminals into the bloodstream.

Oxytocin

When fetal development is complete, the peptide-derived hormone **oxytocin** (tocia- = "childbirth") stimulates uterine contractions and dilation of the cervix. Throughout most of pregnancy, oxytocin hormone receptors are not expressed at high levels in the uterus. Toward the end of pregnancy, the synthesis of oxytocin receptors in the uterus increases, and the smooth muscle cells of the uterus become more sensitive to its effects. Oxytocin is continually released throughout childbirth through a positive feedback mechanism. As noted earlier, oxytocin prompts uterine contractions that push the fetal head toward the cervix. In response, cervical stretching stimulates additional oxytocin to be synthesized by the hypothalamus and released from the pituitary. This increases the intensity and effectiveness of uterine contractions and prompts additional dilation of the cervix. The feedback loop continues until birth.

Although the mother's high blood levels of oxytocin begin to decrease immediately following birth, oxytocin continues to play a role in maternal and newborn health. First, oxytocin is necessary for the milk ejection reflex (commonly referred to as "let-down") in breastfeeding women. As the newborn begins suckling, sensory receptors in the nipples transmit signals to the hypothalamus. In response, oxytocin is secreted and released into the bloodstream. Within seconds, cells in the mother's milk ducts contract, ejecting milk into the infant's mouth. Secondly, in both males and females, oxytocin is thought to contribute to parent—newborn bonding, known as attachment. Oxytocin is also thought to be involved in feelings of love and closeness, as well as in the sexual response.

Antidiuretic Hormone (ADH)

The solute concentration of the blood, or blood osmolarity, may change in response to the consumption of certain foods and fluids, as well as in response to disease, injury, medications, or other factors. Blood osmolarity is constantly monitored by **osmoreceptors**—specialized cells within the hypothalamus that are particularly sensitive to the concentration of sodium ions and other solutes.

In response to high blood osmolarity, which can occur during dehydration or following a very salty meal, the osmoreceptors signal the posterior pituitary to release **antidiuretic hormone** (ADH), also known as vasopressin. The target cells of ADH are located in the tubular cells of the kidneys. Its effect is to increase epithelial permeability to water, allowing increased water reabsorption. The more water reabsorbed from the filtrate, the greater the amount of water that is returned to the blood and the less that is excreted in the urine. A greater concentration of water results in a reduced concentration of solutes. ADH is also known as vasopressin because, in very high concentrations, it causes constriction of blood vessels, which increases blood pressure by increasing peripheral resistance. The release of ADH is controlled by a negative feedback loop. As blood osmolarity decreases, the hypothalamic osmoreceptors sense the change and prompt a corresponding decrease in the secretion of ADH. As a result, less water is reabsorbed from the urine filtrate.

Interestingly, drugs can affect the secretion of ADH. For example, alcohol consumption inhibits the release of ADH, resulting in increased urine production that can eventually lead to dehydration and a hangover. A disease called diabetes insipidus is characterized by chronic underproduction of ADH that causes chronic dehydration. Because little ADH is produced and secreted, not enough water is reabsorbed by the kidneys. Although patients feel thirsty, and increase their fluid consumption, this does not effectively decrease the solute concentration in their blood because ADH levels are not high enough to trigger water reabsorption in the kidneys. Electrolyte imbalances can occur in severe cases of diabetes insipidus.

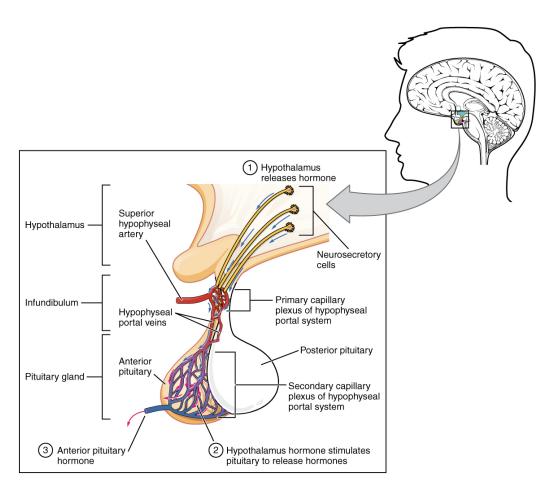
Anterior Pituitary

The anterior pituitary originates from the digestive tract in the embryo and migrates toward the brain during fetal development. There are three regions: the pars distalis is the most anterior, the pars intermedia is adjacent to the posterior pituitary, and the pars tuberalis is a slender "tube" that wraps the infundibulum.

Recall that the posterior pituitary does not synthesize hormones, but merely stores them. In contrast, the anterior pituitary does manufacture hormones. However, the secretion of hormones from the anterior pituitary is regulated by two classes of hormones. These hormones—secreted by the hypothalamus—are the releasing hormones that stimulate the secretion of hormones from the anterior pituitary and the inhibiting hormones that inhibit secretion.

Hypothalamic hormones are secreted by neurons, but enter the anterior pituitary through blood vessels ([link]). Within the infundibulum is a bridge of capillaries that connects the hypothalamus to the anterior pituitary. This network, called the **hypophyseal portal system**, allows hypothalamic hormones to be transported to the anterior pituitary without first entering the systemic circulation. The system originates from the superior hypophyseal artery, which branches off the carotid arteries and transports blood to the hypothalamus. The branches of the superior hypophyseal artery form the hypophyseal portal system (see [link]). Hypothalamic releasing and inhibiting hormones travel through a primary capillary plexus to the portal veins, which carry them into the anterior pituitary. Hormones produced by the anterior pituitary (in response to releasing hormones) enter a secondary capillary plexus, and from there drain into the circulation.

Anterior Pituitary

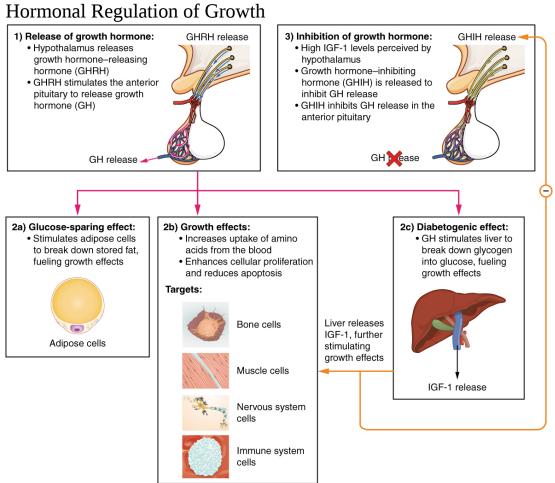


The anterior pituitary manufactures seven hormones. The hypothalamus produces separate hormones that stimulate or inhibit hormone production in the anterior pituitary. Hormones from the hypothalamus reach the anterior pituitary via the hypophyseal portal system.

The anterior pituitary produces seven hormones. These are the growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), beta endorphin, and prolactin. Of the hormones of the anterior pituitary, TSH, ACTH, FSH, and LH are collectively referred to as tropic hormones (trope- = "turning") because they turn on or off the function of other endocrine glands.

Growth Hormone

The endocrine system regulates the growth of the human body, protein synthesis, and cellular replication. A major hormone involved in this process is **growth hormone** (**GH**), also called somatotropin—a protein hormone produced and secreted by the anterior pituitary gland. Its primary function is anabolic; it promotes protein synthesis and tissue building through direct and indirect mechanisms ([link]). GH levels are controlled by the release of GHRH and GHIH (also known as somatostatin) from the hypothalamus.



Growth hormone (GH) directly accelerates the rate of protein synthesis in skeletal muscle and bones. Insulin-like growth factor 1 (IGF-1) is activated by growth hormone and indirectly supports the formation of new proteins in muscle cells and bone.

A glucose-sparing effect occurs when GH stimulates lipolysis, or the breakdown of adipose tissue, releasing fatty acids and glycerol into the blood. Glycerol is transported to the liver and converted to glucose which then enters the plasma. Fatty acids directly enter the plasma and can then be used as an energy source.

GH also initiates the diabetogenic effect in which GH stimulates the liver to break down glycogen to glucose, which is then deposited into the blood. The name "diabetogenic" is derived from the similarity in elevated blood glucose levels observed between individuals with untreated diabetes mellitus and individuals experiencing GH excess. Blood glucose levels rise as the result of a combination of glucose-sparing and diabetogenic effects.

GH indirectly mediates growth and protein synthesis by triggering the liver to produce a group of proteins called **insulin-like growth factors (IGFs)**. These proteins enhance cell division by targeting bone and cartilage and increase protein synthesis when targeting skeletal muscle and inhibit apoptosis, or programmed cell death.

Dysfunction of the endocrine system's control of growth can result in several disorders. For example, **gigantism** is a disorder in children that is caused by the secretion of abnormally large amounts of GH, resulting in excessive growth. A similar condition in adults is **acromegaly**, a disorder that results in the growth of bones in the face, hands, and feet in response to excessive levels of GH in individuals who have stopped growing. Abnormally low levels of GH in children can cause growth impairment—a disorder called **pituitary dwarfism** (also known as growth hormone deficiency).

Thyroid-Stimulating Hormone

The activity of the thyroid gland is regulated by **thyroid-stimulating hormone (TSH)**, also called thyrotropin. TSH is released from the anterior pituitary in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. As discussed shortly, it triggers the secretion of thyroid

hormones by the thyroid gland. In a classic negative feedback loop, elevated levels of thyroid hormones in the bloodstream then trigger a drop in production of TRH and subsequently TSH.

Adrenocorticotropic Hormone

The **adrenocorticotropic hormone** (ACTH), also called corticotropin, stimulates the adrenal cortex to secrete corticosteroid hormones such as cortisol. ACTH comes from a precursor molecule known as propiomelanotropin (POMC) which produces several biologically active molecules when cleaved, including ACTH, melanocyte-stimulating hormone, and the brain opioid peptides known as endorphins.

The release of ACTH is regulated by the corticotropin-releasing hormone (CRH) from the hypothalamus in response to normal physiologic rhythms. A variety of stressors can also influence its release, and the role of ACTH in the stress response is discussed later in this chapter.

Follicle-Stimulating Hormone and Luteinizing Hormone

The endocrine glands secrete a variety of hormones that control the development and regulation of the reproductive system (these glands include the anterior pituitary, the adrenal cortex, and the gonads—the testes in males and the ovaries in females). Much of the development of the reproductive system occurs during puberty and is marked by the development of sex-specific characteristics in both male and female adolescents. Puberty is initiated by gonadotropin-releasing hormone (GnRH), a hormone produced and secreted by the hypothalamus. GnRH stimulates the anterior pituitary to secrete **gonadotropins**—hormones that regulate the function of the gonads. The levels of GnRH are regulated through a negative feedback loop; high levels of reproductive hormones inhibit the release of GnRH. Throughout life, gonadotropins regulate reproductive function and, in the case of women, the onset and cessation of reproductive capacity.

The gonadotropins include two glycoprotein hormones: **follicle-stimulating hormone** (**FSH**) stimulates the production and maturation of sex cells, or gametes, including ova in women and sperm in men. FSH also promotes follicular growth; these follicles then release estrogens in the female ovaries. **Luteinizing hormone** (**LH**) triggers ovulation in women, as well as the production of estrogens and progesterone by the ovaries. LH stimulates production of testosterone by the male testes.

Prolactin

As its name implies, **prolactin (PRL)** promotes lactation (milk production) in women. During pregnancy, it contributes to development of the mammary glands, and after birth, it stimulates the mammary glands to produce breast milk. However, the effects of prolactin depend heavily upon the permissive effects of estrogens, progesterone, and other hormones. And as noted earlier, the let-down of milk occurs in response to stimulation from oxytocin.

In a non-pregnant woman, prolactin secretion is inhibited by prolactin-inhibiting hormone (PIH), which is actually the neurotransmitter dopamine, and is released from neurons in the hypothalamus. Only during pregnancy do prolactin levels rise in response to prolactin-releasing hormone (PRH) from the hypothalamus.

Note:

Everyday Connections

Anabolic Steroids

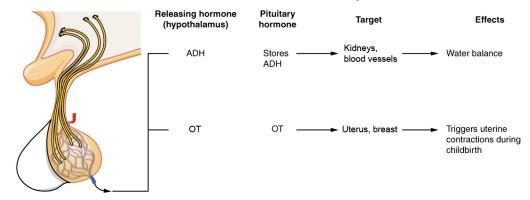
The endocrine system can be exploited for illegal or unethical purposes. A prominent example of this is the use of steroid drugs by professional athletes.

Commonly used for performance enhancement, anabolic steroids are synthetic versions of the male sex hormone, testosterone. By boosting natural levels of this hormone, athletes experience increased muscle mass. Synthetic versions of human growth hormone are also used to build muscle mass.

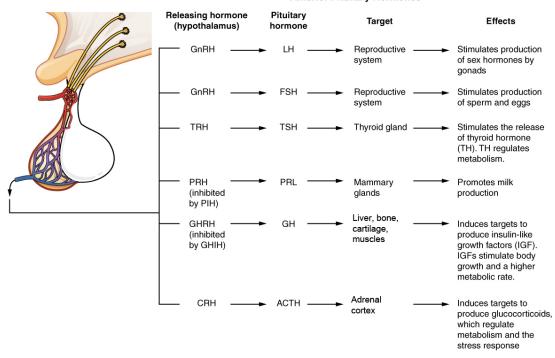
The use of performance-enhancing drugs is banned by all major collegiate and professional sports organizations in the United States because they impart an unfair advantage to athletes who take them. In addition, the drugs can cause significant and dangerous side effects. For example, anabolic steroid use can increase cholesterol levels, raise blood pressure, and damage the liver. Altered testosterone levels (both too low or too high) have been implicated in causing structural damage to the heart, and increasing the risk for cardiac arrhythmias, heart attacks, congestive heart failure, and sudden death. Paradoxically, steroids can have a feminizing effect in males, including shriveled testicles and enlarged breast tissue. In females, their use can cause masculinizing effects such as an enlarged clitoris and growth of facial hair. In both sexes, their use can promote increased aggression (commonly known as "roid-rage"), depression, sleep disturbances, severe acne, and infertility.

Major Pituitary Hormones

Posterior Pituitary Hormones



Anterior Pituitary Hormones



Major pituitary hormones and their target organs.

Note:			



Visit this <u>link</u> to watch an animation showing the role of the hypothalamus and the pituitary gland. Please note thyroxine is also called thyroid hormone. Which hormone is released by the pituitary to stimulate the thyroid gland?

Chapter Review

The hypothalamus—pituitary complex is located in the diencephalon of the brain. The hypothalamus and the pituitary gland are connected by a structure called the infundibulum, which contains vasculature and nerve axons. The pituitary gland is divided into two distinct structures, the anterior and posterior pituitary glands. The posterior lobe houses the axon terminals of hypothalamic neurons. It stores and releases into the bloodstream two hypothalamic hormones: oxytocin and antidiuretic hormone (ADH; also called vasopressin). The anterior lobe is connected to the hypothalamus by vasculature in the infundibulum and produces and secretes six hormones. Their secretion is regulated, however, by releasing and inhibiting hormones from the hypothalamus. The six anterior pituitary hormones are: growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL).

Glossary

acromegaly

disorder in adults caused when abnormally high levels of GH trigger growth of bones in the face, hands, and feet

adrenocorticotropic hormone (ACTH)

anterior pituitary hormone that stimulates the adrenal cortex to secrete corticosteroid hormones (also called corticotropin)

antidiuretic hormone (ADH)

(also known as vasopressin) hypothalamic hormone that is stored by the posterior pituitary and that signals the kidneys to reabsorb water

follicle-stimulating hormone (FSH)

anterior pituitary hormone that stimulates the production and maturation of sex cells

gigantism

disorder in children caused when abnormally high levels of GH prompt excessive growth

gonadotropins

hormones that regulate the function of the gonads

growth hormone (GH)

anterior pituitary hormone that promotes tissue building and influences nutrient metabolism (also called somatotropin)

hypophyseal portal system

network of blood vessels that enables hypothalamic hormones to travel into the anterior lobe of the pituitary without entering the systemic circulation

hypothalamus

region of the diencephalon inferior to the thalamus that functions in neural and endocrine signaling

infundibulum

stalk containing vasculature and neural tissue that connects the pituitary gland to the hypothalamus (also called the pituitary stalk)

insulin-like growth factors (IGF)

protein that enhances cellular proliferation, inhibits apoptosis, and stimulates the cellular uptake of amino acids for protein synthesis

luteinizing hormone (LH)

anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females, and the production of testosterone in males

osmoreceptor

hypothalamic sensory receptor that is stimulated by changes in solute concentration (osmotic pressure) in the blood

oxytocin

hypothalamic hormone stored in the posterior pituitary gland and important in stimulating uterine contractions in labor, milk ejection during breastfeeding, and feelings of attachment (also produced in males)

pituitary dwarfism

disorder in children caused when abnormally low levels of GH result in growth retardation

pituitary gland

bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis)

prolactin (PRL)

anterior pituitary hormone that promotes development of the mammary glands and the production of breast milk

thyroid-stimulating hormone (TSH)

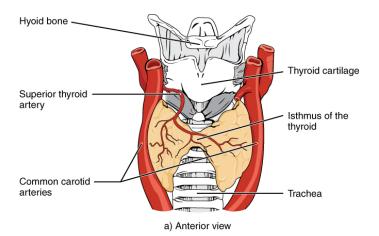
anterior pituitary hormone that triggers secretion of thyroid hormones by the thyroid gland (also called thyrotropin)

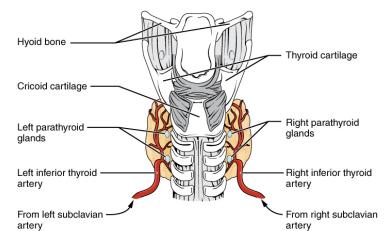
OU Human Physiology: The Thyroid Gland By the end of this section, you will be able to:

- Describe the location and cells of the thyroid gland
- Discuss the synthesis of thyroid hormone(TH)
- Identify the chemical class for thyroid hormone
- Explain the role of thyroid hormones in the regulation of basal metabolism
- Identify the hormone produced by the parafollicular cells of the thyroid
- Discuss the thyroid hormone feedback
- Discuss the target organs for thyroid hormone, the effect TH has on these organs and how plasma solute concentration may change due to TH
- Explain how hypo- or hypersecretion of TH can affect the body
- Identify the chemical class for calcitonin
- Discuss the target organs for calcitonin, the effect of calcitonin has on these organs and how plasma calcium concentration change due to synthesis and secretion of calcitonin
- Describe how calcitonin synthesis and secretion is regulated
- Explain how hypo- and hypersecretion of calcitonin will affect plasma calcium concentration and what impact this may have on body function

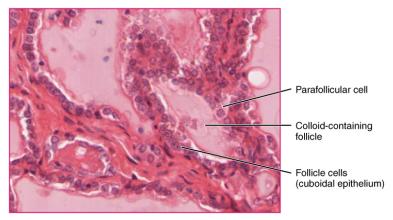
A butterfly-shaped organ, the **thyroid gland** is located anterior to the trachea, just inferior to the larynx ([link]). The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces. The tissue of the thyroid gland is composed mostly of thyroid follicles. The follicles are made up of a central cavity filled with a sticky fluid called **colloid**. Surrounded by a wall of epithelial follicle cells, the colloid is the center of thyroid hormone production, and that production is dependent on the hormones' essential and unique component: iodine.

Thyroid Gland





b) Posterior view



c) Thyroid follicle cells

The thyroid gland is located in the neck where it wraps around the trachea. (a) Anterior view of the thyroid gland. (b) Posterior view of the thyroid gland. (c) The glandular tissue is composed primarily of thyroid follicles. The larger parafollicular cells often appear within the matrix of follicle cells. LM × 1332. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Synthesis and Release of Thyroid Hormones

Hormones are produced in the colloid when atoms of the mineral iodine attach to a glycoprotein, called thyroglobulin, that is secreted into the colloid by the follicle cells. The following steps outline the hormones' assembly:

- 1. Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions (I⁻) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions "trapped" in the follicular cells is many times higher than the concentration in the bloodstream.
- 2. Iodide ions then move to the lumen of the follicle cells that border the colloid. There, the ions undergo oxidation (their negatively charged electrons are removed). The oxidation of two iodide ions (2 I⁻) results in iodine (I₂), which passes through the follicle cell membrane into the colloid.
- 3. In the colloid, peroxidase enzymes link the iodine to the tyrosine amino acids in thyroglobulin to produce two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodines. When one of each of these intermediaries is linked by covalent bonds, the resulting compound is **triiodothyronine** (T_3), a thyroid hormone with three iodines. Much more commonly, two copies of the second intermediary bond, forming tetraiodothyronine, also known as **thyroxine** (T_4), a thyroid hormone with four iodines.

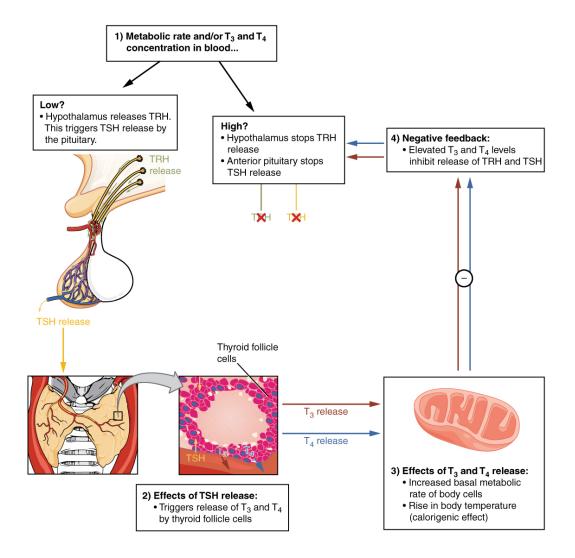
These hormones remain in the colloid center of the thyroid follicles until TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free T_3 and T_4 , which diffuse across the follicle cell membrane and enter the bloodstream.

In the bloodstream, less than one percent of the circulating T_3 and T_4 remains unbound. This free T_3 and T_4 can cross the lipid bilayer of cell membranes and be taken up by cells. The remaining 99 percent of circulating T_3 and T_4 is bound to specialized transport proteins called thyroxine-binding globulins (TBGs), to albumin, or to other plasma proteins. This "packaging" prevents their free diffusion into body cells. When blood levels of T_3 and T_4 begin to decline, bound T_3 and T_4 are released from these plasma proteins and readily cross the membrane of target cells. T_3 is more potent than T_4 , and many cells convert T_4 to T_3 through the removal of an iodine atom.

Regulation of TH Synthesis

The release of T_3 and T_4 from the thyroid gland is regulated by thyroidstimulating hormone (TSH). As shown in [link], low blood levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete T_3 and T_4 . The levels of TRH, TSH, T_3 , and T_4 are regulated by a negative feedback system in which increasing levels of T_3 and T_4 decrease the production and secretion of TSH, and TRH.

Classic Negative Feedback Loop



A classic negative feedback loop controls the regulation of thyroid hormone levels.

Functions of Thyroid Hormones

The thyroid hormones, T_3 and T_4 , are often referred to as metabolic hormones because their levels influence the body's basal metabolic rate, the amount of energy used by the body at rest. When T_3 and T_4 bind to intracellular receptors located on the mitochondria, they cause an increase in nutrient breakdown and the use of oxygen to produce ATP. In addition, T_3 and T_4 initiate the transcription of genes involved in glucose oxidation.

Although these mechanisms prompt cells to produce more ATP, the process is inefficient, and an abnormally increased level of heat is released as a byproduct of these reactions. This so-called calorigenic effect (calor= "heat") raises body temperature.

Adequate levels of thyroid hormones are also required for protein synthesis and for fetal and childhood tissue development and growth. They are especially critical for normal development of the nervous system both in utero and in early childhood, and they continue to support neurological function in adults. As noted earlier, these thyroid hormones have a complex interrelationship with reproductive hormones, and deficiencies can influence libido, fertility, and other aspects of reproductive function. Finally, thyroid hormones increase the body's sensitivity to catecholamines (epinephrine and norepinephrine) from the adrenal medulla by upregulation of receptors in the blood vessels. When levels of T_3 and T_4 hormones are excessive, this effect accelerates the heart rate, strengthens the heartbeat, and increases blood pressure. Because thyroid hormones regulate metabolism, heat production, protein synthesis, and many other body functions, thyroid disorders can have severe and widespread consequences.

Note:

Disorders of the...

Endocrine System: Iodine Deficiency, Hypothyroidism, and Hyperthyroidism

As discussed above, dietary iodine is required for the synthesis of T_3 and T_4 . But for much of the world's population, foods do not provide adequate levels of this mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Marine fish and shrimp tend to have high levels because they concentrate iodine from seawater, but many people in landlocked regions lack access to seafood. Thus, the primary source of dietary iodine in many countries is iodized salt. Fortification of salt with iodine began in the United States in 1924, and international efforts to iodize salt in the world's poorest nations continue today.

Dietary iodine deficiency can result in the impaired ability to synthesize T_3 and T_4 , leading to a variety of severe disorders. When T_3 and T_4 cannot be produced, TSH is secreted in increasing amounts. As a result of this hyperstimulation, thyroglobulin accumulates in the thyroid gland follicles, increasing their deposits of colloid. The accumulation of colloid increases the overall size of the thyroid gland, a condition called a **goiter** ([link]). A goiter is only a visible indication of the deficiency. Other iodine deficiency disorders include impaired growth and development, decreased fertility, and prenatal and infant death. Moreover, iodine deficiency is the primary cause of preventable mental retardation worldwide. **Neonatal hypothyroidism** (cretinism) is characterized by cognitive deficits, short stature, and sometimes deafness and muteness in children and adults born to mothers who were iodine-deficient during pregnancy.

Goiter



(credit: "Almazi"/Wikimedia Commons)

In areas of the world with access to iodized salt, dietary deficiency is rare. Instead, inflammation of the thyroid gland is the more common cause of low blood levels of thyroid hormones. Called **hypothyroidism**, the condition is characterized by a low metabolic rate, weight gain, cold extremities, constipation, reduced libido, menstrual irregularities, and reduced mental activity. In contrast, **hyperthyroidism**—an abnormally

elevated blood level of thyroid hormones—is often caused by a pituitary or thyroid tumor. In Graves' disease, the hyperthyroid state results from an autoimmune reaction in which antibodies overstimulate the follicle cells of the thyroid gland. Hyperthyroidism can lead to an increased metabolic rate, excessive body heat and sweating, diarrhea, weight loss, tremors, and increased heart rate. The person's eyes may bulge (called exophthalmos) as antibodies produce inflammation in the soft tissues of the orbits. The person may also develop a goiter.

Calcitonin

The thyroid gland also secretes a hormone called **calcitonin** that is produced by the parafollicular cells (also called C cells) that stud the tissue between distinct follicles. Calcitonin is released in response to a rise in blood calcium levels. It appears to have a function in decreasing blood calcium concentrations by:

- Targeting bone to inhibit the activity of osteoclasts, bone cells that release calcium into the circulation by degrading bone matrix
- Targeting bone to increase osteoblastic activity
- Targeting the intestines to decrease calcium absorption in the intestines
- Targeting kidneys to increase calcium loss in the urine

However, these functions are usually not significant in maintaining calcium homeostasis, so the importance of calcitonin is not entirely understood. Pharmaceutical preparations of calcitonin are sometimes prescribed to reduce osteoclast activity in people with osteoporosis and to reduce the degradation of cartilage in people with osteoarthritis. The hormones secreted by thyroid are summarized in [link].

Thyroid Hormones				
Associated hormones	Chemical class	Effect		
Thyroxine (T_4) , triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate		
Calcitonin	Peptide	Reduces blood Ca ²⁺ levels		

Of course, calcium is critical for many other biological processes. It is a second messenger in many signaling pathways, and is essential for muscle contraction, nerve impulse transmission, and blood clotting. Given these roles, it is not surprising that blood calcium levels are tightly regulated by the endocrine system. The organs involved in the regulation are the parathyroid glands.

Chapter Review

The thyroid gland is a butterfly-shaped organ located in the neck anterior to the trachea. Its hormones regulate basal metabolism, oxygen use, nutrient metabolism, the production of ATP, and calcium homeostasis. They also contribute to normal growth and development of body tissues, including maturation of the nervous system, and they increase the body's sensitivity to catecholamines. The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are produced and secreted by the thyroid gland in response to thyroid-stimulating hormone (TSH) from the anterior pituitary. Synthesis of the amino acid—derived T3 and T4 hormones requires iodine. Insufficient amounts of iodine in the diet can lead to goiter, cretinism, and many other disorders.

Glossary

calcitonin

peptide hormone produced and secreted by the parafollicular cells (C cells) of the thyroid gland that functions to decrease blood calcium levels

colloid

viscous fluid in the central cavity of thyroid follicles, containing the glycoprotein thyroglobulin

goiter

enlargement of the thyroid gland either as a result of iodine deficiency or hyperthyroidism

hyperthyroidism

clinically abnormal, elevated level of thyroid hormone in the blood; characterized by an increased metabolic rate, excess body heat, sweating, diarrhea, weight loss, and increased heart rate

hypothyroidism

clinically abnormal, low level of thyroid hormone in the blood; characterized by low metabolic rate, weight gain, cold extremities, constipation, and reduced mental activity

neonatal hypothyroidism

condition characterized by cognitive deficits, short stature, and other signs and symptoms in people born to women who were iodine-deficient during pregnancy

thyroid gland

large endocrine gland responsible for the synthesis of thyroid hormones

thyroxine

(also, tetraiodothyronine, T_4) amino acid—derived thyroid hormone that is more abundant but less potent than T_3 and often converted to T_3 by target cells

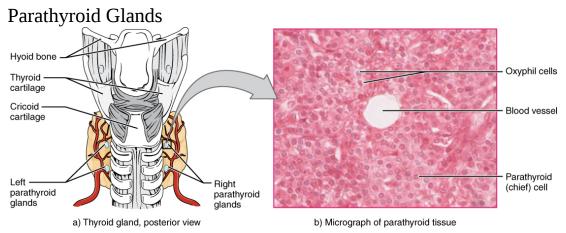
triiodothyronine

(also, $T_{3})$ amino acid–derived thyroid hormone that is less abundant but more potent than $T_{4}\,$

OU Human Physiology: The Parathyroid Glands By the end of this section, you will be able to:

- Describe the location and structure of the parathyroid glands
- Discuss the target organs for parathyroid hormone (PTH), the effect of PTH has on these organs and how plasma calcium concentration change due to synthesis and secretion of PTH
- Describe how PTH is synthesis and secretion is regulated
- Discuss the physiological response of parathyroid dysfunction

The **parathyroid glands** are tiny, round structures usually found embedded in the posterior surface of the thyroid gland ([link]). A thick connective tissue capsule separates the glands from the thyroid tissue. Most people have four parathyroid glands, but occasionally there are more in tissues of the neck or chest. The function of one type of parathyroid cells, the oxyphil cells, is not clear. The primary functional cells of the parathyroid glands are the chief cells. These epithelial cells produce and secrete the **parathyroid hormone (PTH)**, the major hormone involved in the regulation of blood calcium levels.



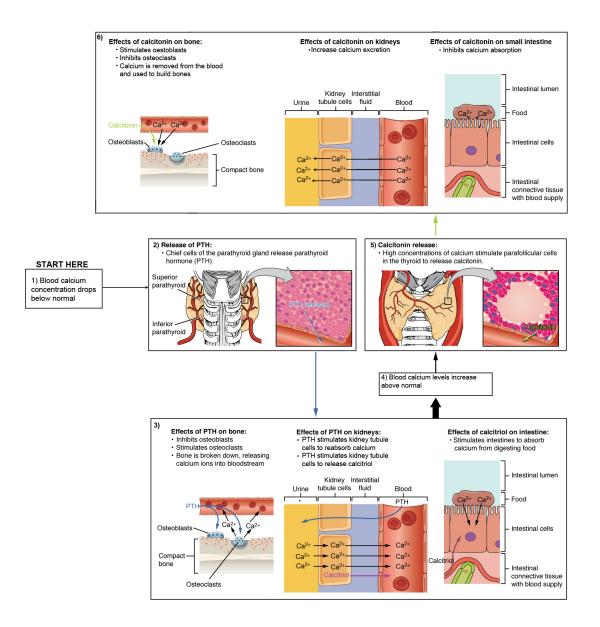
The small parathyroid glands are embedded in the posterior surface of the thyroid gland. LM \times 760. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the University of Michigan WebScope at http://141.214.65.171/Histology/Endocrine%20System/217 HISTO 40X.s vs/view.apml to explore the tissue sample in greater detail.

The parathyroid glands produce and secrete PTH, a peptide hormone, in response to low blood calcium levels ([link]). PTH secretion causes the release of calcium from the bones by stimulating osteoclasts, which secrete enzymes that degrade bone and release calcium into the interstitial fluid. PTH also inhibits osteoblasts, the cells involved in bone deposition, thereby sparing blood calcium. PTH causes increased reabsorption of calcium (and magnesium) in the kidney tubules from the urine filtrate. In addition, PTH initiates the production of the steroid hormone calcitriol (also known as 1,25-dihydroxyvitamin D), which is the active form of vitamin D_3 , in the kidneys. Calcitriol then stimulates increased absorption of dietary calcium by the intestines. A negative feedback loop regulates the levels of PTH, with rising blood calcium levels inhibiting further release of PTH. Parathyroid Hormone in Maintaining Blood Calcium Homeostasis



Parathyroid hormone increases blood calcium levels when they drop too low. Conversely, calcitonin, which is released from the thyroid gland, decreases blood calcium levels when they become too high. These two mechanisms constantly maintain blood calcium concentration at homeostasis.

Abnormally high activity of the parathyroid gland can cause **hyperparathyroidism**, a disorder caused by an overproduction of PTH that results in excessive calcium reabsorption from bone. Hyperparathyroidism

can significantly decrease bone density, leading to spontaneous fractures or deformities. As blood calcium levels rise, cell membrane permeability to sodium is decreased, and the responsiveness of the nervous system is reduced. At the same time, calcium deposits may collect in the body's tissues and organs, impairing their functioning.

In contrast, abnormally low blood calcium levels may be caused by parathyroid hormone deficiency, called **hypoparathyroidism**, which may develop following injury or surgery involving the thyroid gland. Low blood calcium increases membrane permeability to sodium, resulting in muscle twitching, cramping, spasms, or convulsions. Severe deficits can paralyze muscles, including those involved in breathing, and can be fatal.

When blood calcium levels are high, calcitonin is produced and secreted by the parafollicular cells of the thyroid gland. As discussed earlier, calcitonin inhibits the activity of osteoclasts, reduces the absorption of dietary calcium in the intestine, and signals the kidneys to reabsorb less calcium, resulting in larger amounts of calcium excreted in the urine.

Chapter Review

Calcium is required for a variety of important physiologic processes, including neuromuscular functioning; thus, blood calcium levels are closely regulated. The parathyroid glands are small structures located on the posterior thyroid gland that produce parathyroid hormone (PTH), which regulates blood calcium levels. Low blood calcium levels cause the production and secretion of PTH. In contrast, elevated blood calcium levels inhibit secretion of PTH and trigger secretion of the thyroid hormone calcitonin. Underproduction of PTH can result in hypoparathyroidism. In contrast, overproduction of PTH can result in hypoparathyroidism.

Glossary

hyperparathyroidism

disorder caused by overproduction of PTH that results in abnormally elevated blood calcium

hypoparathyroidism

disorder caused by underproduction of PTH that results in abnormally low blood calcium

parathyroid glands

small, round glands embedded in the posterior thyroid gland that produce parathyroid hormone (PTH)

parathyroid hormone (PTH)

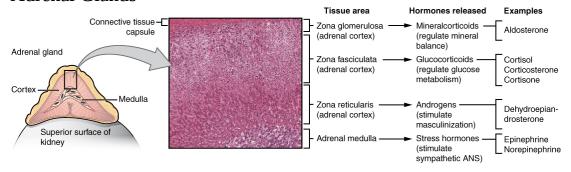
peptide hormone produced and secreted by the parathyroid glands in response to low blood calcium levels

OU Human Physiology: The Adrenal Glands By the end of this section, you will be able to:

- Describe the location and structure of the adrenal glands.
- Identify the hormones produced by the adrenal cortex and adrenal medulla, and summarize their target cells and effects.
- Identify the chemical class for each adrenal hormone.
- For each of the adrenal hormones discuss the target organs, the effect of the hormone on the target organ, and how the plasma solute concentration may change due to the synthesis and secretion of these hormones.
- Describe how adrenal hormones' synthesis and secretion are regulated.
- Explain how hypo- or hypersecretion of adrenal hormones will impact body function (homeostasis).

The **adrenal glands** are wedges of glandular and neuroendocrine tissue adhering to the top of the kidneys by a fibrous capsule ([link]). The adrenal glands have a rich blood supply and experience one of the highest rates of blood flow in the body. They are served by several arteries branching off the aorta, including the suprarenal and renal arteries. Blood flows to each adrenal gland at the adrenal cortex and then drains into the adrenal medulla. Adrenal hormones are released into the circulation via the left and right suprarenal veins.

Adrenal Glands



Both adrenal glands sit atop the kidneys and are composed of an outer cortex and an inner medulla, all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of

hormones. LM × 204. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the University of Michigan WebScope at http://141.214.65.171/Histology/Endocrine%20System/New%20Scans/230 HISTO 40x.svs/view.apml to explore the tissue sample in greater detail.

The adrenal gland consists of an outer cortex of glandular tissue and an inner medulla of nervous tissue. The cortex itself is divided into three zones: the **zona glomerulosa**, the **zona fasciculata**, and the **zona reticularis**. Each region secretes its own set of hormones.

The **adrenal cortex**, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol. This pathway will be discussed in more detail below.

The **adrenal medulla** is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the

medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

One of the major functions of the adrenal gland is to respond to stress. Stress can be either physical or psychological or both. Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. Psychological stresses include the perception of a physical threat, a fight with a loved one, or just a bad day at school.

The body responds in different ways to short-term stress and long-term stress following a pattern known as the **general adaptation syndrome** (GAS). Stage one of GAS is called the **alarm reaction**. This is short-term stress, the fight-or-flight response, mediated by the hormones epinephrine and norepinephrine from the adrenal medulla via the SAM pathway. Their function is to prepare the body for extreme physical exertion. Once this stress is relieved, the body quickly returns to normal. The section on the adrenal medulla covers this response in more detail.

If the stress is not soon relieved, the body adapts to the stress in the second stage called the **stage of resistance**. If a person is starving for example, the body may send signals to the gastrointestinal tract to maximize the absorption of nutrients from food.

If the stress continues for a longer term, a condition called chronic stress, however, the body responds with symptoms quite different than the fight-or-flight response. During the **stage of exhaustion**, individuals may begin to suffer depression, the suppression of their immune response, severe fatigue, or even a fatal heart attack. These symptoms are mediated by the hormones of the adrenal cortex, especially cortisol, released as a result of signals from the HPA axis.

Adrenal hormones also have several non—stress-related functions, including the increase of blood sodium and glucose levels, which will be described in detail below.

Adrenal Cortex

The adrenal cortex consists of multiple layers of lipid-storing cells that occur in three structurally distinct regions. Each of these regions produces different hormones.

Note:



Visit this <u>link</u> to view an animation describing the location and function of the adrenal glands. Which hormone produced by the adrenal glands is responsible for the mobilization of energy stores?

Hormones of the Zona Glomerulosa

The most superficial region of the adrenal cortex is the zona glomerulosa, which produces a group of hormones collectively referred to as **mineralocorticoids** because of their effect on body minerals, especially sodium and potassium. These hormones are essential for fluid and electrolyte balance.

Aldosterone is the major mineralocorticoid. It is important in the regulation of the concentration of sodium and potassium ions in urine, sweat, and saliva. For example, it is released in response to elevated blood K^+ , low blood Na^+ , low blood pressure, or low blood volume. In response, aldosterone increases the excretion of K^+ and the retention of Na^+ via reabsorption by the kidneys, which in turn increases blood volume and blood pressure.

Aldosterone is also a key component of the renin-angiotensin-aldosterone system (RAAS) in which specialized cells of the kidneys secrete the enzyme renin in response to low blood volume or low blood pressure.

Hormones of the Zona Fasciculata

The intermediate region of the adrenal cortex is the zona fasciculata, named as such because the cells form small fascicles (bundles) separated by tiny blood vessels. The cells of the zona fasciculata produce hormones called **glucocorticoids** because of their role in glucose metabolism. The most important of these is **cortisol**, some of which the liver converts to cortisone. A glucocorticoid produced in much smaller amounts is corticosterone. In response to long-term stressors, the hypothalamus secretes CRH, which in turn triggers the release of ACTH by the anterior pituitary. ACTH triggers the release of the glucocorticoids. Their overall effect is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies.

In conditions of long-term stress cortisol promotes the catabolism of glycogen to glucose, the catabolism of stored triglycerides into fatty acids and glycerol, and the catabolism of muscle proteins into amino acids. These raw materials can then be used to synthesize additional glucose and ketones for use as body fuels. The hippocampus, which is part of the temporal lobe of the cerebral cortices and important in memory formation, is highly sensitive to stress levels because of its many glucocorticoid receptors.

You are probably familiar with prescription and over-the-counter medications containing glucocorticoids, such as cortisone injections into inflamed joints, prednisone tablets and steroid-based inhalers used to manage severe asthma, and hydrocortisone creams applied to relieve itchy skin rashes. These drugs reflect another role of cortisol—the downregulation of the immune system, which inhibits the inflammatory response.

Hormones of the Zona Reticularis

The deepest region of the adrenal cortex is the zona reticularis, which produces small amounts of a class of steroid sex hormones called androgens. During puberty and most of adulthood, androgens are produced in the gonads. The androgens produced in the zona reticularis supplement the gonadal androgens. They are produced in response to ACTH from the anterior pituitary and are converted in the tissues to testosterone or estrogens. In adult women, they may contribute to the sex drive, but their function in adult men is not well understood. In post-menopausal women, as the functions of the ovaries decline, the main source of estrogens becomes the androgens produced by the zona reticularis.

Adrenal Medulla

As noted earlier, the adrenal cortex releases glucocorticoids in response to long-term stress such as severe illness. In contrast, the adrenal medulla releases its hormones in response to acute, short-term stress mediated by the sympathetic nervous system (SNS).

The medullary tissue is composed of unique postganglionic SNS neurons called **chromaffin** cells, which are large and irregularly shaped, and produce the **epinephrine** (also called adrenaline) and **norepinephrine** (or noradrenaline). Epinephrine is produced in greater quantities—approximately a 4 to 1 ratio with norepinephrine—and is the more powerful hormone. Because the chromaffin cells release epinephrine and norepinephrine into the systemic circulation, where they travel widely and exert effects on distant cells, they are considered hormones. Derived from the amino acid tyrosine, they are chemically classified as catecholamines.

The secretion of medullary epinephrine and norepinephrine is controlled by a neural pathway that originates from the hypothalamus in response to danger or stress (the SAM pathway). Both epinephrine and norepinephrine signal the liver and skeletal muscle cells to convert glycogen into glucose, resulting in increased blood glucose levels. These hormones increase the heart rate, pulse, and blood pressure to prepare the body to fight the perceived threat or flee from it. In addition, the pathway dilates the airways,

raising blood oxygen levels. It also prompts vasodilation, further increasing the oxygenation of important organs such as the lungs, brain, heart, and skeletal muscle. At the same time, it triggers vasoconstriction to blood vessels serving less essential organs such as the gastrointestinal tract, kidneys, and skin, and downregulates some components of the immune system. Other effects include a dry mouth, loss of appetite, pupil dilation, and a loss of peripheral vision. The major hormones of the adrenal glands are summarized in [link].

Hormones of the Adrenal Glands				
Adrenal gland	Associated hormones	Chemical class	Effect	
Adrenal cortex	Aldosterone	Steroid	Increases blood Na ⁺ levels	
Adrenal cortex	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels	
Adrenal medulla	Epinephrine, norepinephrine	Amine	Stimulate fight- or-flight response	

Disorders Involving the Adrenal Glands

Several disorders are caused by the dysregulation of the hormones produced by the adrenal glands. For example, Cushing's disease is a disorder characterized by high blood glucose levels and the accumulation of lipid deposits on the face and neck. It is caused by hypersecretion of cortisol. The most common source of Cushing's disease is a pituitary tumor that secretes cortisol or ACTH in abnormally high amounts. Other common signs of Cushing's disease include the development of a moon-shaped face, a buffalo hump on the back of the neck, rapid weight gain, and hair loss. Chronically elevated glucose levels are also associated with an elevated risk of developing type 2 diabetes. In addition to hyperglycemia, chronically elevated glucocorticoids compromise immunity, resistance to infection, and memory, and can result in rapid weight gain and hair loss.

In contrast, the hyposecretion of corticosteroids can result in Addison's disease, a rare disorder that causes low blood glucose levels and low blood sodium levels. The signs and symptoms of Addison's disease are vague and are typical of other disorders as well, making diagnosis difficult. They may include general weakness, abdominal pain, weight loss, nausea, vomiting, sweating, and cravings for salty food.

Chapter Review

The adrenal glands, located superior to each kidney, consist of two regions: the adrenal cortex and adrenal medulla. The adrenal cortex—the outer layer of the gland—produces mineralocorticoids, glucocorticoids, and androgens. The adrenal medulla at the core of the gland produces epinephrine and norepinephrine.

The adrenal glands mediate a short-term stress response and a long-term stress response. A perceived threat results in the secretion of epinephrine and norepinephrine from the adrenal medulla, which mediate the fight-or-flight response. The long-term stress response is mediated by the secretion of CRH from the hypothalamus, which triggers ACTH, which in turn stimulates the secretion of corticosteroids from the adrenal cortex. The mineralocorticoids, chiefly aldosterone, cause sodium and fluid retention, which increases blood volume and blood pressure.

Glossary

adrenal cortex

outer region of the adrenal glands consisting of multiple layers of epithelial cells and capillary networks that produces mineralocorticoids and glucocorticoids

adrenal glands

endocrine glands located at the top of each kidney that are important for the regulation of the stress response, blood pressure and blood volume, water homeostasis, and electrolyte levels

adrenal medulla

inner layer of the adrenal glands that plays an important role in the stress response by producing epinephrine and norepinephrine

alarm reaction

the short-term stress, or the fight-or-flight response, of stage one of the general adaptation syndrome mediated by the hormones epinephrine and norepinephrine

aldosterone

hormone produced and secreted by the adrenal cortex that stimulates sodium and fluid retention and increases blood volume and blood pressure

chromaffin

neuroendocrine cells of the adrenal medulla

cortisol

glucocorticoid important in gluconeogenesis, the catabolism of glycogen, and downregulation of the immune system

epinephrine

primary and most potent catecholamine hormone secreted by the adrenal medulla in response to short-term stress; also called adrenaline

general adaptation syndrome (GAS)

the human body's three-stage response pattern to short- and long-term stress

glucocorticoids

hormones produced by the zona fasciculata of the adrenal cortex that influence glucose metabolism

mineralocorticoids

hormones produced by the zona glomerulosa cells of the adrenal cortex that influence fluid and electrolyte balance

norepinephrine

secondary catecholamine hormone secreted by the adrenal medulla in response to short-term stress; also called noradrenaline

stage of exhaustion

stage three of the general adaptation syndrome; the body's long-term response to stress mediated by the hormones of the adrenal cortex

stage of resistance

stage two of the general adaptation syndrome; the body's continued response to stress after stage one diminishes

zona fasciculata

intermediate region of the adrenal cortex that produce hormones called glucocorticoids

zona glomerulosa

most superficial region of the adrenal cortex, which produces the hormones collectively referred to as mineralocorticoids

zona reticularis

deepest region of the adrenal cortex, which produces the steroid sex hormones called androgens

OU Human Physiology: The Pineal Gland By the end of this section, you will be able to:

- Describe the location and structure of the pineal gland
- Identify chemical class for melatonin
- Discuss the function of melatonin

Recall that the hypothalamus, part of the diencephalon of the brain, sits inferior and somewhat anterior to the thalamus. Inferior but somewhat posterior to the thalamus is the **pineal gland**, a tiny endocrine gland whose functions are not entirely clear. The **pinealocyte** cells that make up the pineal gland are known to produce and secrete the amine hormone **melatonin**, which is derived from serotonin.

The secretion of melatonin varies according to the level of light received from the environment. When photons of light stimulate the retinas of the eyes, a nerve impulse is sent to a region of the hypothalamus called the suprachiasmatic nucleus (SCN), which is important in regulating biological rhythms. From the SCN, the nerve signal is carried to the spinal cord and eventually to the pineal gland, where the production of melatonin is inhibited. As a result, blood levels of melatonin fall, promoting wakefulness. In contrast, as light levels decline—such as during the evening —melatonin production increases, boosting blood levels and causing drowsiness.

Note:



Visit this <u>link</u> to view an animation describing the function of the hormone melatonin. What should you avoid doing in the middle of your sleep cycle that would lower melatonin?

The secretion of melatonin may influence the body's circadian rhythms, the dark-light fluctuations that affect not only sleepiness and wakefulness, but also appetite and body temperature. Interestingly, children have higher melatonin levels than adults, which may prevent the release of gonadotropins from the anterior pituitary, thereby inhibiting the onset of puberty. Finally, an antioxidant role of melatonin is the subject of current research.

Jet lag occurs when a person travels across several time zones and feels sleepy during the day or wakeful at night. Traveling across multiple time zones significantly disturbs the light-dark cycle regulated by melatonin. It can take up to several days for melatonin synthesis to adjust to the light-dark patterns in the new environment, resulting in jet lag. Some air travelers take melatonin supplements to induce sleep.

Chapter Review

The pineal gland is an endocrine structure of the diencephalon of the brain, and is located inferior and posterior to the thalamus. It is made up of pinealocytes. These cells produce and secrete the hormone melatonin in response to low light levels. High blood levels of melatonin induce drowsiness. Jet lag, caused by traveling across several time zones, occurs because melatonin synthesis takes several days to readjust to the light-dark patterns in the new environment.

Glossary

melatonin

amino acid—derived hormone that is secreted in response to low light and causes drowsiness

pineal gland

endocrine gland that secretes melatonin, which is important in regulating the sleep-wake cycle

pinealocyte

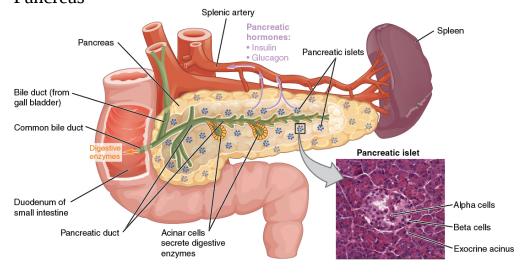
cell of the pineal gland that produces and secretes the hormone melatonin

OU Human Physiology: The Endocrine Pancreas By the end of this section, you will be able to:

- Describe the location and structure of the pancreas, and the morphology and function of the pancreatic islets
- Compare and contrast the functions of insulin and glucagon
- Identify the chemical class for insulin and glucagon
- For both insulin and glucagon, discuss the target organs, the effect of the hormones on the target organ and how the plasma solute concentration may change due to synthesis and secretion of these hormones
- Discuss how insulin and glucagon synthesis and secretion is regulated
- Explain how hypo- or hypersecretion of these hormones will impact homeostasis

The **pancreas** is a long, slender organ, most of which is located posterior to the bottom half of the stomach ([link]). Although it is primarily an exocrine gland, secreting a variety of digestive enzymes, the pancreas has an endocrine function. Its **pancreatic islets**—clusters of cells formerly known as the islets of Langerhans—secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).

Pancreas



The pancreatic exocrine function involves the acinar cells secreting digestive enzymes that are transported into the small intestine by the pancreatic duct. Its

endocrine function involves the secretion of insulin (produced by beta cells) and glucagon (produced by alpha cells) within the pancreatic islets. These two hormones regulate the rate of glucose metabolism in the body. The micrograph reveals pancreatic islets. LM × 760. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the University of Michigan WebScope at http://141.214.65.171/Histology/Digestive%20System/Liver%20and%20P ancreas/188B HISTO 40X.svs/view.apml to explore the tissue sample in greater detail.

Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of cells:

- The **alpha cell** produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation.
- The **beta cell** produces the hormone insulin and makes up approximately 75 percent of each islet.
- The **delta cell** accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Recall that somatostatin is also

- released by the hypothalamus (as GHIH), and the stomach and intestines also secrete it. An inhibiting hormone, pancreatic somatostatin inhibits the release of both glucagon and insulin.
- The PP cell accounts for about one percent of islet cells and secretes
 the pancreatic polypeptide hormone. It is thought to play a role in
 appetite, as well as in the regulation of pancreatic exocrine and
 endocrine secretions. Pancreatic polypeptide released following a meal
 may reduce further food consumption; however, it is also released in
 response to fasting.

Regulation of Blood Glucose Levels by Insulin and Glucagon

Glucose is required for cellular respiration and is the preferred fuel for all body cells. The body derives glucose from the breakdown of the carbohydrate-containing foods and drinks we consume. Glucose not immediately taken up by cells for fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in the adipose tissue. Hormones regulate both the storage and the utilization of glucose as required. Receptors located in the pancreas sense blood glucose levels, and subsequently the pancreatic cells secrete glucagon or insulin to maintain normal levels. During the absorptive or fed state, insulin will be synthesized and secreted. Insulin promotes anabolism by increasing glucose oxidation, increasing glycogen synthesis, increasing lipogenesis, and increasing protein synthesis. Following the absorptive state, the post absorptive or fasted state when there is no food intake insulin synthesis and secretion will discontinue, and glucagon will be synthesized and secreted. Glucagon will increase glycogenolysis, increase gluconeogenesis, and increase ketogenesis. Thus, the actions of glucagon are antagonistic to insulin.

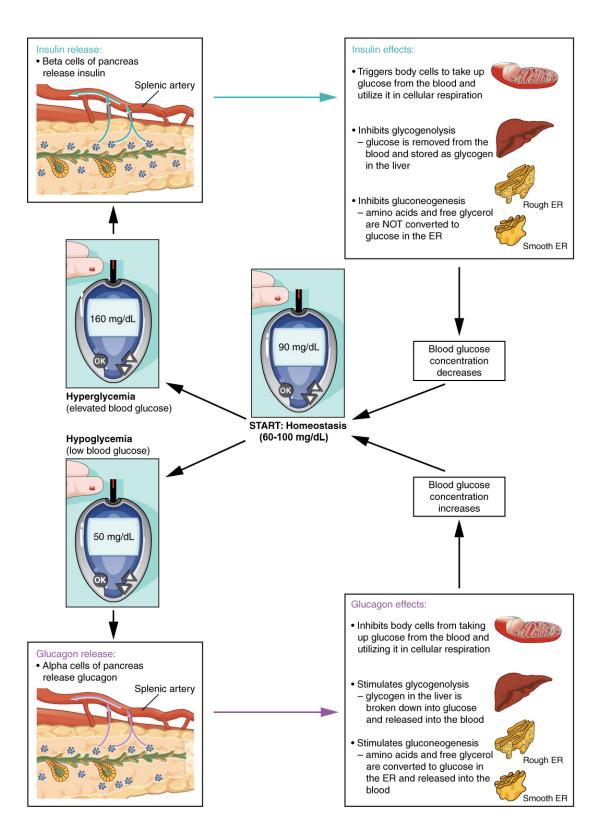
Glucagon

Receptors in the pancreas can sense the decline in blood glucose levels, such as during periods of fasting (post absorptive state) or during prolonged labor or exercise ([link]). In response, the alpha cells of the pancreas secrete the hormone **glucagon**, which has several effects:

- It stimulates the liver to convert its stores of glycogen back into glucose. This response is known as glycogenolysis. The glucose is then released into the circulation for use by body cells ([link]).
- It stimulates the liver to take up amino acids, lactate, and pyruvate from the blood and convert them into glucose. This response is known as gluconeogenesis.
- It stimulates lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol. Some of the free glycerol released into the bloodstream travels to the liver, which converts it into glucose. This is also a form of gluconeogenesis.
- During periods of prolonged fasting, fatty acids produced via lipolysis can be converted to ketones and used by brain and peripheral tissues.

Taken together, these actions increase blood glucose levels. The activity of glucagon is regulated through a negative feedback mechanism; rising blood glucose levels inhibit further glucagon production and secretion.

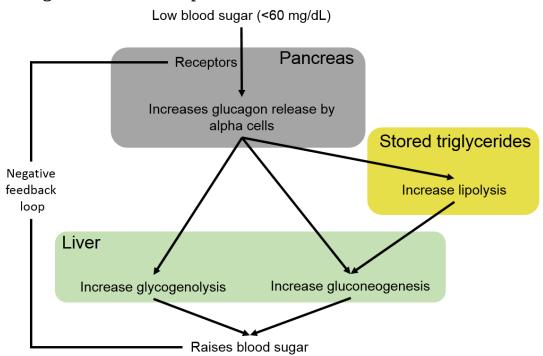
Homeostatic Regulation of Blood Glucose Levels



Blood glucose concentration is tightly maintained between 60 mg/dL and 100 mg/dL. If blood glucose concentration rises

above this range, insulin is released, which stimulates body cells to remove glucose from the blood. If blood glucose concentration drops below this range, glucagon is released, which stimulates body cells to release glucose into the blood.

Glucagon Feedback Loop



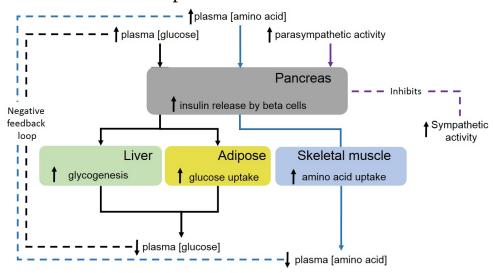
Glucagon secreted from alpha cells in the pancreas is responsible for raising blood glucose levels to return to normal values.

Insulin

Insulin promotes anabolism, thus its primary function is to facilitate the uptake of glucose into body cells. Red blood cells, as well as cells of the brain, liver, kidneys, and the lining of the small intestine, do not have

insulin receptors on their cell membranes and do not require insulin for glucose uptake. Although all other body cells do require insulin if they are to take glucose from the bloodstream, the liver, skeletal muscle and adipose are the primary targets of insulin.

Insulin Feedback Loop



Insulin secreted from beta cells in the pancreas is responsible for lowering blood glucose levels to return to normal values (less than 100mg/dL).

The presence of food in the intestine triggers the release of gastrointestinal tract hormones such as glucose-dependent insulinotropic peptide (previously known as gastric inhibitory peptide). This is in turn the initial trigger for insulin production and secretion by the beta cells of the pancreas. Once nutrient absorption occurs, the resulting surge in blood glucose levels further stimulates insulin secretion.

Precisely how insulin facilitates glucose uptake is not entirely clear. However, insulin appears to activate a tyrosine kinase receptor, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing facilitative glucose transporters to the cell membrane. In the absence of insulin, these transport proteins are normally recycled slowly

between the cell membrane and cell interior. Insulin triggers the rapid movement of a pool of glucose transporter vesicles to the cell membrane, where they fuse and expose the glucose transporters to the extracellular fluid. The transporters then move glucose by facilitated diffusion into the cell interior.

Note:



Visit this <u>link</u> to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

Insulin also reduces blood glucose levels by stimulating glycolysis, the metabolism of glucose for generation of ATP. Moreover, it stimulates the liver to convert excess glucose into glycogen (a process called glycogenesis) for storage, and it inhibits enzymes involved in glycogenolysis and gluconeogenesis. Finally, insulin promotes triglyceride and protein synthesis. The secretion of insulin is regulated through a negative feedback mechanism. As blood glucose levels decrease, further insulin release is inhibited. The pancreatic hormones are summarized in [link].

Hormones of the Pancreas				
Associated hormones	Chemical class	Effect		
Insulin (beta cells)	Protein	Reduces blood glucose levels		
Glucagon (alpha cells)	Protein	Increases blood glucose levels		
Somatostatin (delta cells)	Protein	Inhibits insulin and glucagon release		
Pancreatic polypeptide (PP cells)	Protein	Role in appetite		

Note:

Disorders of the...

Endocrine System: Diabetes Mellitus

Dysfunction of insulin production and secretion, as well as the target cells' responsiveness to insulin, can lead to a condition called **diabetes mellitus**. An increasingly common disease, diabetes mellitus has been diagnosed in more than 18 million adults in the United States, and more than 200,000 children. It is estimated that up to 7 million more adults have the condition but have not been diagnosed. In addition, approximately 79 million people in the US are estimated to have pre-diabetes, a condition in which blood glucose levels are abnormally high, but not yet high enough to be classified as diabetes.

There are two main forms of diabetes mellitus. Type 1 diabetes is an autoimmune disease affecting the beta cells of the pancreas. Certain genes are recognized to increase susceptibility. The beta cells of people with type 1 diabetes do not produce insulin; thus, synthetic insulin must be

administered by injection or infusion. This form of diabetes accounts for less than five percent of all diabetes cases.

Type 2 diabetes accounts for approximately 95 percent of all cases. It is acquired, and lifestyle factors such as poor diet, inactivity, and the presence of pre-diabetes greatly increase a person's risk. About 80 to 90 percent of people with type 2 diabetes are overweight or obese. In type 2 diabetes, cells become resistant to the effects of insulin. In response, the pancreas increases its insulin secretion, but over time, the beta cells become exhausted. In many cases, type 2 diabetes can be reversed by moderate weight loss, regular physical activity, and consumption of a healthy diet; however, if blood glucose levels cannot be controlled, the diabetic will eventually require insulin.

Two of the early manifestations of diabetes are excessive urination and excessive thirst. They demonstrate how the out-of-control levels of glucose in the blood affect kidney function. The kidneys are responsible for filtering glucose from the blood. Excessive blood glucose draws water into the urine, and as a result the person eliminates an abnormally large quantity of sweet urine. The use of body water to dilute the urine leaves the body dehydrated, and so the person is unusually and continually thirsty. The person may also experience persistent hunger because the body cells are unable to access the glucose in the bloodstream.

Over time, persistently high levels of glucose in the blood injure tissues throughout the body, especially those of the blood vessels and nerves. Inflammation and injury of the lining of arteries lead to atherosclerosis and an increased risk of heart attack and stroke. Damage to the microscopic blood vessels of the kidney impairs kidney function and can lead to kidney failure. Damage to blood vessels that serve the eyes can lead to blindness. Blood vessel damage also reduces circulation to the limbs, whereas nerve damage leads to a loss of sensation, called neuropathy, particularly in the hands and feet. Together, these changes increase the risk of injury, infection, and tissue death (necrosis), contributing to a high rate of toe, foot, and lower leg amputations in people with diabetes. Uncontrolled diabetes can also lead to a dangerous form of metabolic acidosis called ketoacidosis. Deprived of glucose, cells increasingly rely on fat stores for fuel. However, in a glucose-deficient state, the liver is forced to use an alternative lipid metabolism pathway that results in the increased production of ketone bodies (or ketones), which are acidic. The build-up of ketones in the blood causes ketoacidosis, which—if left untreated—may lead to a life-threatening "diabetic coma." Together, these complications make diabetes the seventh leading cause of death in the United States. Diabetes is diagnosed when lab tests reveal that blood glucose levels are higher than normal, a condition called **hyperglycemia**. The treatment of diabetes depends on the type, the severity of the condition, and the ability of the patient to make lifestyle changes. As noted earlier, moderate weight loss, regular physical activity, and consumption of a healthful diet can reduce blood glucose levels. Some patients with type 2 diabetes may be unable to control their disease with these lifestyle changes, and will require medication. Historically, the first-line treatment of type 2 diabetes was insulin. Research advances have resulted in alternative options, including medications that enhance pancreatic function.

Note:



Visit this <u>link</u> to view an animation describing the role of insulin and the pancreas in diabetes.

Chapter Review

The pancreas has both exocrine and endocrine functions. The pancreatic islet cell types include alpha cells, which produce glucagon; beta cells, which produce insulin; delta cells, which produce somatostatin; and PP cells, which produce pancreatic polypeptide. Insulin and glucagon are involved in the regulation of glucose metabolism. Insulin is produced by the beta cells in response to high blood glucose levels. It enhances glucose

uptake and utilization by target cells, as well as the storage of excess glucose for later use. Dysfunction of the production of insulin or target cell resistance to the effects of insulin causes diabetes mellitus, a disorder characterized by high blood glucose levels. The hormone glucagon is produced and secreted by the alpha cells of the pancreas in response to low blood glucose levels. Glucagon stimulates mechanisms that increase blood glucose levels, such as the catabolism of glycogen into glucose.

Glossary

alpha cell

pancreatic islet cell type that produces the hormone glucagon

beta cell

pancreatic islet cell type that produces the hormone insulin

delta cell

minor cell type in the pancreas that secretes the hormone somatostatin

diabetes mellitus

condition caused by destruction or dysfunction of the beta cells of the pancreas or cellular resistance to insulin that results in abnormally high blood glucose levels

glucagon

pancreatic hormone that stimulates the catabolism of glycogen to glucose, thereby increasing blood glucose levels

hyperglycemia

abnormally high blood glucose levels

insulin

pancreatic hormone that enhances the cellular uptake and utilization of glucose, thereby decreasing blood glucose levels

pancreas

organ with both exocrine and endocrine functions located posterior to the stomach that is important for digestion and the regulation of blood

glucose

pancreatic islets

specialized clusters of pancreatic cells that have endocrine functions; also called islets of Langerhans

PP cell

minor cell type in the pancreas that secretes the hormone pancreatic polypeptide

OU Human Physiology: Organs with Secondary Endocrine Functions By the end of this section, you will be able to:

 Identify the organs with a secondary endocrine function and the hormone they produce

Here, you will learn about the hormone-producing activities of the heart, gastrointestinal tract, kidneys, skeleton, adipose tissue, skin, and thymus.

Heart

When the body experiences an increase in blood volume or pressure, the cells of the heart's atrial wall stretch. In response, specialized cells in the wall of the atria produce and secrete the peptide hormone **atrial natriuretic peptide (ANP)**. ANP signals the kidneys to reduce sodium reabsorption, thereby decreasing the amount of water reabsorbed from the urine filtrate and reducing blood volume. Other actions of ANP include the inhibition of renin secretion and the initiation of the renin-angiotensin-aldosterone system (RAAS) and vasodilation. Therefore, ANP aids in decreasing blood pressure, blood volume, and blood sodium levels.

Gastrointestinal Tract

The endocrine cells of the GI tract are located in the mucosa of the stomach and small intestine. Some of these hormones are secreted in response to eating a meal and aid in digestion. An example of a hormone secreted by the stomach cells is gastrin, a peptide hormone secreted in response to stomach distention that stimulates the release of hydrochloric acid. Secretin is a peptide hormone secreted by the small intestine as acidic chyme (partially digested food and fluid) moves from the stomach. It stimulates the release of bicarbonate from the pancreas, which buffers the acidic chyme, and inhibits the further secretion of hydrochloric acid by the stomach. Cholecystokinin (CCK) is another peptide hormone released from the small intestine. It promotes the secretion of pancreatic enzymes and the release of bile from the gallbladder, both of which facilitate digestion. Other hormones produced by the intestinal cells aid in glucose metabolism, such as by stimulating the pancreatic beta cells to secrete insulin, reducing

glucagon secretion from the alpha cells, or enhancing cellular sensitivity to insulin.

Kidneys

The kidneys participate in several complex endocrine pathways and produce certain hormones. A decline in blood flow to the kidneys stimulates them to release the enzyme renin, triggering the reninangiotensin-aldosterone (RAAS) system, and stimulating the reabsorption of sodium and water. The reabsorption increases blood flow and blood pressure. The kidneys also play a role in regulating blood calcium levels through the production of calcitriol from vitamin D₃, which is released in response to the secretion of parathyroid hormone (PTH). In addition, the kidneys produce the hormone **erythropoietin** (**EPO**) in response to low oxygen levels. EPO stimulates the production of red blood cells (erythrocytes) in the bone marrow, thereby increasing oxygen delivery to tissues. You may have heard of EPO as a performance-enhancing drug (in a synthetic form).

Skeleton

Although bone has long been recognized as a target for hormones, only recently have researchers recognized that the skeleton itself produces at least two hormones. Fibroblast growth factor 23 (FGF23) is produced by bone cells in response to increased blood levels of vitamin D_3 or phosphate. It triggers the kidneys to inhibit the formation of calcitriol from vitamin D_3 and to increase phosphorus excretion. Osteocalcin, produced by osteoblasts, stimulates the pancreatic beta cells to increase insulin production. It also acts on peripheral tissues to increase their sensitivity to insulin and their utilization of glucose.

Adipose Tissue

Adipose tissue produces and secretes several hormones involved in lipid metabolism and storage. One important example is **leptin**, a protein manufactured by adipose cells that circulates in amounts directly

proportional to levels of body fat. Leptin is released in response to food consumption and acts by binding to brain neurons involved in energy intake and expenditure. Binding of leptin produces a feeling of satiety after a meal, thereby reducing appetite. It also appears that the binding of leptin to brain receptors triggers the sympathetic nervous system to regulate bone metabolism, increasing deposition of cortical bone. Adiponectin—another hormone synthesized by adipose cells—appears to reduce cellular insulin resistance and to protect blood vessels from inflammation and atherosclerosis. Its levels are lower in people who are obese, and rise following weight loss.

Skin

The skin functions as an endocrine organ in the production of the inactive form of vitamin D₃, cholecalciferol. When cholesterol present in the epidermis is exposed to ultraviolet radiation, it is converted to cholecalciferol, which then enters the blood. In the liver, cholecalciferol is converted to an intermediate that travels to the kidneys and is further converted to calcitriol, the active form of vitamin D₃. Vitamin D is important in a variety of physiological processes, including intestinal calcium absorption and immune system function. In some studies, low levels of vitamin D have been associated with increased risks of cancer, severe asthma, and multiple sclerosis. Vitamin D deficiency in children causes rickets, and in adults, osteomalacia—both of which are characterized by bone deterioration.

Thymus

The **thymus** is an organ of the immune system that is larger and more active during infancy and early childhood, and begins to atrophy as we age. Its endocrine function is the production of a group of hormones called **thymosins** that contribute to the development and differentiation of T lymphocytes, which are immune cells. Although the role of thymosins is not yet well understood, it is clear that they contribute to the immune response. Thymosins have been found in tissues other than the thymus and

have a wide variety of functions, so the thymosins cannot be strictly categorized as thymic hormones.

Liver

The liver is responsible for secreting at least four important hormones or hormone precursors: insulin-like growth factor (somatomedin), angiotensinogen, thrombopoetin, and hepcidin. Insulin-like growth factor-1 is the immediate stimulus for growth in the body, especially of the bones. Angiotensinogen is the precursor to angiotensin, mentioned earlier, which increases blood pressure. Thrombopoetin stimulates the production of the blood's platelets. Hepcidins block the release of iron from cells in the body, helping to regulate iron homeostasis in our body fluids. The major hormones of these other organs are summarized in [link].

Organs with Secondary Endocrine Functions and Their Major Hormones				
Organ	Major hormones	Effects		
Heart	Atrial natriuretic peptide (ANP)	Reduces blood volume, blood pressure, and Na ⁺ concentration		
Gastrointestinal tract	Gastrin, secretin, and cholecystokinin	Aid digestion of food and buffering of stomach acids		

Organs with Secondary Endocrine Functions and Their Major Hormones

Organ	Major hormones	Effects	
Gastrointestinal tract	Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1)	Stimulate beta cells of the pancreas to release insulin	
Kidneys	Renin	Stimulates release of aldosterone	
Kidneys	Calcitriol	Aids in the absorption of Ca ²⁺	
Kidneys	Erythropoietin	Triggers the formation of red blood cells in the bone marrow	
Skeleton	FGF23	Inhibits production of calcitriol and increases phosphate excretion	
Skeleton	Osteocalcin	Increases insulin production	
Adipose tissue	Leptin	Promotes satiety signals in the brain	
Adipose tissue	Adiponectin	Reduces insulin resistance	

Organs with Secondary Endocrine Functions and Their Major Hormones				
Organ	Major hormones	Effects		
Skin	Cholecalciferol	Modified to form vitamin D		
Thymus (and other organs)	Thymosins	Among other things, aids in the development of T lymphocytes of the immune system		
Liver	Insulin-like growth factor-1	Stimulates bodily growth		
Liver	Angiotensinogen	Raises blood pressure		
Liver	Thrombopoetin	Causes increase in platelets		
Liver	Hepcidin	Blocks release of iron into body fluids		

Chapter Review

Some organs have a secondary endocrine function. For example, the walls of the atria of the heart produce the hormone atrial natriuretic peptide (ANP), the gastrointestinal tract produces the hormones gastrin, secretin, and cholecystokinin, which aid in digestion, and the kidneys produce erythropoietin (EPO), which stimulates the formation of red blood cells. Even bone, adipose tissue, and the skin have secondary endocrine functions.

Glossary

atrial natriuretic peptide (ANP)

peptide hormone produced by the walls of the atria in response to high blood pressure, blood volume, or blood sodium that reduces the reabsorption of sodium and water in the kidneys and promotes vasodilation

erythropoietin (EPO)

protein hormone secreted in response to low oxygen levels that triggers the bone marrow to produce red blood cells

leptin

protein hormone secreted by adipose tissues in response to food consumption that promotes satiety

thymosins

hormones produced and secreted by the thymus that play an important role in the development and differentiation of T cells

thymus

organ that is involved in the development and maturation of T-cells and is particularly active during infancy and childhood

OU Human Physiology: Development and Aging of the Endocrine System By the end of this section, you will be able to:

• Discuss the effects of aging on the endocrine system

As the body ages, changes occur that affect the endocrine system, sometimes altering the production, secretion, and catabolism of hormones. For example, the structure of the anterior pituitary gland changes as vascularization decreases and the connective tissue content increases with increasing age. This restructuring affects the gland's hormone production. For example, the amount of human growth hormone that is produced declines with age, resulting in the reduced muscle mass commonly observed in the elderly.

The adrenal glands also undergo changes as the body ages; as fibrous tissue increases, the production of cortisol and aldosterone decreases. Interestingly, the production and secretion of epinephrine and norepinephrine remain normal throughout the aging process.

A well-known example of the aging process affecting an endocrine gland is menopause and the decline of ovarian function. With increasing age, the ovaries decrease in both size and weight and become progressively less sensitive to gonadotropins. This gradually causes a decrease in estrogen and progesterone levels, leading to menopause and the inability to reproduce. Low levels of estrogens and progesterone are also associated with some disease states, such as osteoporosis, atherosclerosis, and hyperlipidemia, or abnormal blood lipid levels.

Testosterone levels also decline with age, a condition called andropause (or viropause); however, this decline is much less dramatic than the decline of estrogens in women, and much more gradual, rarely affecting sperm production until very old age. Although this means that males maintain their ability to father children for decades longer than females, the quantity, quality, and motility of their sperm is often reduced.

As the body ages, the thyroid gland produces less of the thyroid hormones, causing a gradual decrease in the basal metabolic rate. The lower metabolic rate reduces the production of body heat and increases levels of body fat.

Parathyroid hormones, on the other hand, increase with age. This may be because of reduced dietary calcium levels, causing a compensatory increase in parathyroid hormone. However, increased parathyroid hormone levels combined with decreased levels of calcitonin (and estrogens in women) can lead to osteoporosis as PTH stimulates demineralization of bones to increase blood calcium levels. Notice that osteoporosis is common in both elderly males and females.

Increasing age also affects glucose metabolism, as blood glucose levels spike more rapidly and take longer to return to normal in the elderly. In addition, increasing glucose intolerance may occur because of a gradual decline in cellular insulin sensitivity. Almost 27 percent of Americans aged 65 and older have diabetes.

Chapter Review

The endocrine system originates from all three germ layers of the embryo, including the endoderm, ectoderm, and mesoderm. In general, different hormone classes arise from distinct germ layers. Aging affects the endocrine glands, potentially affecting hormone production and secretion, and can cause disease. The production of hormones, such as human growth hormone, cortisol, aldosterone, sex hormones, and the thyroid hormones, decreases with age.

OU Human Physiology: Neural Communication Introduction class="introduction" Robotic Arms Playing Foosball

As the neural circuitry of the nervous system has become more fully understood and robotics more sophisticated, it is now possible to integrate technology with the body and restore abilities following traumatic events. At some point in the future, will this type of technology lead to the ability to augment our nervous systems? (credit: U.S. Army/Wikimedi a Commons)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Identify the anatomical and functional divisions of the nervous system
- Describe the organization of the nervous system and function for each component in the system
- Relate the functional and structural differences between gray matter and white matter structures of the nervous system to the structure of neurons
- Describe the basic structure of a neuron to include types and function of gated channels
- Identify the different types of neurons on the basis of polarity
- List the glial cells of the CNS and PNS and describe their function

- Distinguish the major functions of the nervous system: sensation (stimuli), integration, and response
- Describe the components of the membrane that establish the resting membrane potential
- Describe the changes that occur to the membrane that result in the action potential
- Discuss refractory periods
- Discuss graded potentials including their purpose, location on the neuron, and types
- Compare and contrast the types of summation
- Categorize the neurotransmitters by chemical type and effect

The nervous system is a very complex organ system. In Peter D. Kramer's book *Listening to Prozac*, a pharmaceutical researcher is quoted as saying, "If the human brain were simple enough for us to understand, we would be too simple to understand it" (1994). That quote is from the early 1990s; in the two decades since, progress has continued at an amazing rate within the scientific disciplines of neuroscience. It is an interesting conundrum to consider that the complexity of the nervous system may be too complex for it (that is, for us) to completely unravel. But our current level of understanding is probably nowhere close to that limit.

One easy way to begin to understand the structure of the nervous system is to start with the large divisions and work through to a more in-depth understanding. In other chapters, the finer details of the nervous system will be explained, but first looking at an overview of the system will allow you to begin to understand how its parts work together. The focus of this chapter is on nervous (neural) tissue, both its structure and its function. But before you learn about that, you will see a big picture of the system—actually, a few big pictures.

OU Human Physiology: Basic Structure and Function of the Nervous System

By the end of this section, you will be able to:

- Identify the anatomical and functional divisions of the nervous system.
- Describe the organization of the nervous system.
- Discuss the function of each component of the organization of the nervous system.
- Relate the functional and structural differences between gray matter and white matter structures of the nervous system to the structure of neurons.
- List the basic functions of the nervous system.

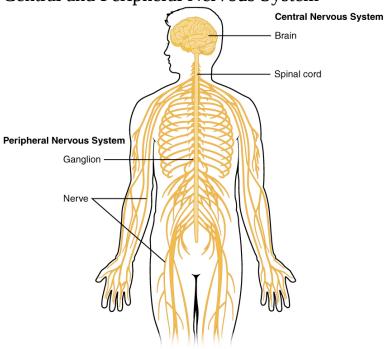
The picture you have in your mind of the nervous system probably includes the **brain**, the nervous tissue contained within the cranium, and the **spinal cord**, the extension of nervous tissue within the vertebral column. That suggests it is made of two organs—and you may not even think of the spinal cord as an organ—but the nervous system is a very complex structure. Within the brain, many different and separate regions are responsible for many different and separate functions. It is as if the nervous system is composed of many organs that all look similar and can only be differentiated using tools such as the microscope or electrophysiology. In comparison, it is easy to see that the stomach is different than the esophagus or the liver, so you can imagine the digestive system as a collection of specific organs.

The Central and Peripheral Nervous Systems

The nervous system can be divided into two major regions: the central and peripheral nervous systems. The **central nervous system (CNS)** is the brain and spinal cord, and the **peripheral nervous system (PNS)** is everything else ([link]). The brain is contained within the cranial cavity of the skull, and the spinal cord is contained within the vertebral cavity of the vertebral column. It is a bit of an oversimplification to say that the CNS is what is inside these two cavities and the peripheral nervous system is outside of them, but that is one way to start to think about it. In actuality, there are some elements of the peripheral nervous system that are within the

cranial or vertebral cavities. The peripheral nervous system is so named because it is on the periphery—meaning beyond the brain and spinal cord. Depending on different aspects of the nervous system, the dividing line between central and peripheral is not necessarily universal.

Central and Peripheral Nervous System



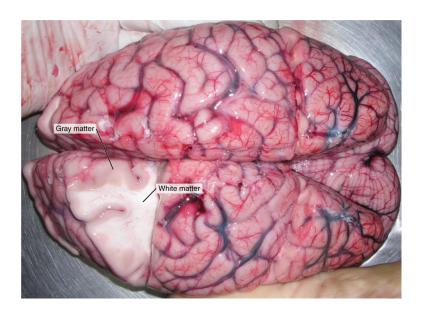
The structures of the PNS are referred to as ganglia and nerves, which can be seen as distinct structures. The equivalent structures in the CNS are not obvious from this overall perspective and are best examined in prepared tissue under the microscope.

Nervous tissue, present in both the CNS and PNS, contains two basic types of cells: neurons and glial cells. A **glial cell** is one of a variety of cells that provide a framework of tissue that supports the neurons and their activities. The **neuron** is the more functionally important of the two, in terms of the communicative function of the nervous system. To describe the functional divisions of the nervous system, it is important to understand the structure

of a neuron. Neurons are cells and therefore have a **soma**, or cell body, but they also have extensions of the cell; each extension is generally referred to as a **process**. There is one important process that every neuron has called an **axon**, which is the fiber that connects a neuron with its target. Another type of process that branches off from the soma is the **dendrite**. Dendrites are responsible for receiving most of the input from other neurons. Looking at nervous tissue, there are regions that predominantly contain cell bodies and regions that are largely composed of just axons. These two regions within nervous system structures are often referred to as **gray matter** (the regions with many cell bodies and dendrites) or **white matter** (the regions with many axons). [link] demonstrates the appearance of these regions in the brain and spinal cord. The colors ascribed to these regions are what would be seen in "fresh," or unstained, nervous tissue. Gray matter is not necessarily gray. It can be pinkish because of blood content, or even slightly tan, depending on how long the tissue has been preserved. But white matter is white because axons are insulated by a lipid-rich substance called **myelin**. Lipids can appear as white ("fatty") material, much like the fat on a raw piece of chicken or beef. Actually, gray matter may have that color ascribed to it because next to the white matter, it is just darker—hence, gray.

The distinction between gray matter and white matter is most often applied to central nervous tissue, which has large regions that can be seen with the unaided eye. When looking at peripheral structures, often a microscope is used and the tissue is stained with artificial colors. That is not to say that central nervous tissue cannot be stained and viewed under a microscope, but unstained tissue is most likely from the CNS—for example, a frontal section of the brain or cross section of the spinal cord.

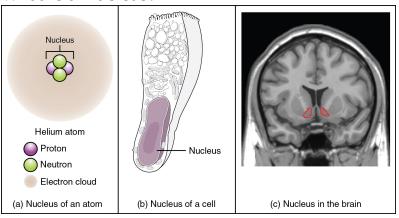
Gray Matter and White Matter



A brain removed during an autopsy, with a partial section removed, shows white matter surrounded by gray matter. Gray matter makes up the outer cortex of the brain. (credit: modification of work by "Suseno"/Wikimedia Commons)

Regardless of the appearance of stained or unstained tissue, the cell bodies of neurons or axons can be located in discrete anatomical structures that need to be named. Those names are specific to whether the structure is central or peripheral. A localized collection of neuron cell bodies in the CNS is referred to as a **nucleus**. In the PNS, a cluster of neuron cell bodies is referred to as a **ganglion**. [link] indicates how the term nucleus has a few different meanings within anatomy and physiology. It is the center of an atom, where protons and neutrons are found; it is the center of a cell, where the DNA is found; and it is a center of some function in the CNS. There is also a potentially confusing use of the word ganglion (plural = ganglia) that has a historical explanation. In the central nervous system, there is a group of nuclei that are connected together and were once called the basal ganglia before "ganglion" became accepted as a description for a peripheral structure. Some sources refer to this group of nuclei as the "basal nuclei" to avoid confusion.

What Is a Nucleus?

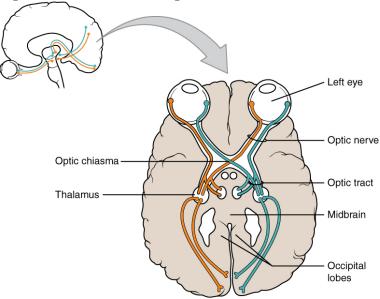


(a) The nucleus of an atom contains its protons and neutrons. (b) The nucleus of a cell is the organelle that contains DNA. (c) A nucleus in the CNS is a localized center of function with the cell bodies of several neurons, shown here circled in red. (credit c: "Was a bee"/Wikimedia Commons)

Terminology applied to bundles of axons also differs depending on location. A bundle of axons, or fibers, found in the CNS is called a **tract** whereas the same thing in the PNS would be called a **nerve**. There is an important point to make about these terms, which is that they can both be used to refer to the same bundle of axons. When those axons are in the PNS, the term is nerve, but if they are CNS, the term is tract. The most obvious example of this is the axons that project from the retina into the brain. Those axons are called the optic nerve as they leave the eye, but when they are inside the cranium, they are referred to as the optic tract. There is a specific place where the name changes, which is the optic chiasm, but they are still the same axons ([link]). A similar situation outside of science can be described for some roads. Imagine a road called "Broad Street" in a town called "Anyville." The road leaves Anyville and goes to the next town over, called "Hometown." When the road crosses the line between the two towns and is in Hometown, its name changes to "Main Street." That is the idea behind the naming of the retinal axons. In the PNS, they are called the optic nerve,

and in the CNS, they are the optic tract. [link] helps to clarify which of these terms apply to the central or peripheral nervous systems.

Optic Nerve Versus Optic Tract



This drawing of the connections of the eye to the brain shows the optic nerve extending from the eye to the chiasm, where the structure continues as the optic tract. The same axons extend from the eye to the brain through these two bundles of fibers, but the chiasm represents the border between peripheral and central.

Note:



In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic resonance imaging (MRI). This is a tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique in the nervous system is that fat tissue and water appear as different shades between black and white. Because white matter is fatty (from myelin) and gray matter is not, they can be easily distinguished in MRI images. Visit the Nobel Prize web site to play an interactive game that demonstrates the use of this technology and compares it with other types of imaging technologies. Also, the results from an MRI session are compared with images obtained from X-ray or computed tomography. How do the imaging techniques shown in this game indicate the separation of white and gray matter compared with the freshly dissected tissue shown earlier?

Structures of the CNS and PNS				
	CNS	PNS		
Group of Neuron Cell Bodies (i.e., gray matter)	Nucleus	Ganglion		
Bundle of Axons (i.e., white matter)	Tract	Nerve		

Functional Divisions of the Nervous System

The nervous system can also be divided on the basis of its functions, but anatomical divisions and functional divisions are different. The CNS and the PNS both contribute to the same functions, but those functions can be attributed to different regions of the brain (such as the cerebral cortex or the hypothalamus) or to different ganglia in the periphery. The problem with

trying to fit functional differences into anatomical divisions is that sometimes the same structure can be part of several functions. For example, the optic nerve carries signals from the retina that are either used for the conscious perception of visual stimuli, which takes place in the cerebral cortex, or for the reflexive responses of smooth muscle tissue that are processed through the hypothalamus.

There are two ways to consider how the nervous system is divided functionally. First, the basic functions of the nervous system are sensation, integration, and response. Secondly, control of the body can be somatic or autonomic—divisions that are largely defined by the structures that are involved in the response. There is also a region of the peripheral nervous system that is called the enteric nervous system that is responsible for a specific set of the functions within the realm of autonomic control related to gastrointestinal functions.

Basic Functions

The nervous system is involved in receiving information about the environment around us (sensation) and generating responses to that information (motor responses). The nervous system can be divided into regions that are responsible for **sensation** (sensory functions) and for the **response** (motor functions). But there is a third function that needs to be included. Sensory input needs to be integrated with other sensations, as well as with memories, emotional state, or learning (cognition). Some regions of the nervous system are termed **integration** or association areas. The process of integration combines sensory perceptions and higher cognitive functions such as memories, learning, and emotion to produce a response.

Sensation. The first major function of the nervous system is sensation—receiving information about the environment to gain input about what is happening outside the body (or, sometimes, within the body). The sensory functions of the nervous system register the presence of a change from homeostasis or a particular event in the environment, known as a **stimulus**. The senses we think of most are the "big five": taste, smell, touch, sight, and hearing. The stimuli for taste and smell are both chemical substances

(molecules, compounds, ions, etc.), touch is physical or mechanical stimuli that interact with the skin, sight is light stimuli, and hearing is the perception of sound, which is a physical stimulus similar to some aspects of touch. There are actually more senses than just those, but that list represents the major senses. Those five are all senses that receive stimuli from the outside world, and of which there is conscious perception. Additional sensory stimuli might be from the internal environment (inside the body), such as the stretch of an organ wall or the concentration of certain ions in the blood.

Response. The nervous system produces a response on the basis of the stimuli perceived by sensory structures. An obvious response would be the movement of muscles, such as withdrawing a hand from a hot stove, but there are broader uses of the term. The nervous system can cause the contraction of all three types of muscle tissue. For example, skeletal muscle contracts to move the skeleton, cardiac muscle is influenced as heart rate increases during exercise, and smooth muscle contracts as the digestive system moves food along the digestive tract. Responses also include the neural control of glands in the body as well, such as the production and secretion of sweat by the eccrine and merocrine sweat glands found in the skin to lower body temperature.

Responses can be divided into those that are voluntary or conscious (contraction of skeletal muscle) and those that are involuntary (contraction of smooth muscles, regulation of cardiac muscle, activation of glands). Voluntary responses are governed by the somatic nervous system and involuntary responses are governed by the autonomic nervous system, which are discussed in the next section.

Integration. Stimuli that are received by sensory structures are communicated to the nervous system where that information is processed. This is called integration. Stimuli are compared with, or integrated with, other stimuli, memories of previous stimuli, or the state of a person at a particular time. This leads to the specific response that will be generated. Seeing a baseball pitched to a batter will not automatically cause the batter to swing. The trajectory of the ball and its speed will need to be considered. Maybe the count is three balls and one strike, and the batter wants to let this

pitch go by in the hope of getting a walk to first base. Or maybe the batter's team is so far ahead, it would be fun to just swing away.

Controlling the Body

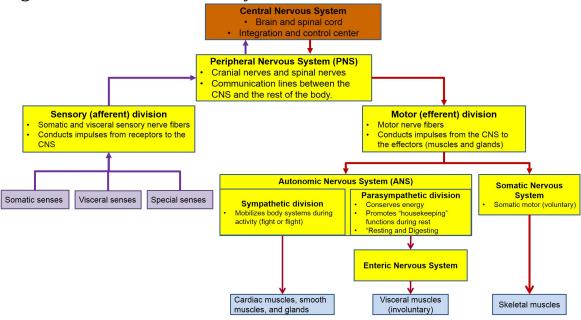
The nervous system can be divided into two parts mostly on the basis of a functional difference in responses. The **somatic nervous system (SNS)** is responsible for conscious perception and voluntary motor responses. Voluntary motor response means the contraction of skeletal muscle, but those contractions are not always voluntary in the sense that you have to want to perform them. Some somatic motor responses are reflexes, and often happen without a conscious decision to perform them. If your friend jumps out from behind a corner and yells "Boo!" you will be startled and you might scream or leap back. You didn't decide to do that, and you may not have wanted to give your friend a reason to laugh at your expense, but it is a reflex involving skeletal muscle contractions. Other motor responses become automatic (in other words, unconscious) as a person learns motor skills (referred to as "habit learning" or "procedural memory").

The **autonomic nervous system (ANS)** is responsible for involuntary control of the body, usually for the sake of homeostasis (regulation of the internal environment). Sensory input for autonomic functions can be from sensory structures tuned to external or internal environmental stimuli. The motor output extends to smooth and cardiac muscle as well as glandular tissue. The role of the autonomic system is to regulate the organ systems of the body, which usually means to control homeostasis. Sweat glands, for example, are controlled by the autonomic system. When you are hot, sweating helps cool your body down. That is a homeostatic mechanism. But when you are nervous, you might start sweating also. That is not homeostatic, it is the physiological response to an emotional state.

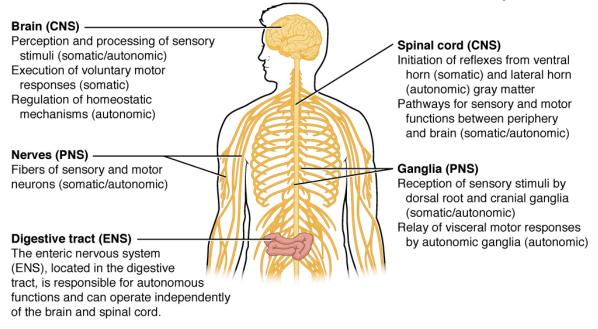
There is another division of the nervous system that describes functional responses. The **enteric nervous system (ENS)** is responsible for controlling the smooth muscle and glandular tissue in your digestive system. It is a large part of the PNS, and is not dependent on the CNS. It is sometimes valid, however, to consider the enteric system to be a part of the

autonomic system because the neural structures that make up the enteric system are a component of the autonomic output that regulates digestion. There are some differences between the two, but for our purposes here there will be a good bit of overlap. See [link] for examples of where these divisions of the nervous system can be found.

Organization of the Nervous Systems



Somatic, Autonomic, and Enteric Structures of the Nervous System



Somatic structures include the spinal nerves, both motor and

sensory fibers, as well as the sensory ganglia (posterior root ganglia and cranial nerve ganglia). Autonomic structures are found in the nerves also, but include the sympathetic and parasympathetic ganglia. The enteric nervous system includes the nervous tissue within the organs of the digestive tract.

Note:



Visit this <u>site</u> to read about a woman that notices that her daughter is having trouble walking up the stairs. This leads to the discovery of a hereditary condition that affects the brain and spinal cord. The electromyography and MRI tests indicated deficiencies in the spinal cord and cerebellum, both of which are responsible for controlling coordinated movements. To what functional division of the nervous system would these structures belong?

Note:

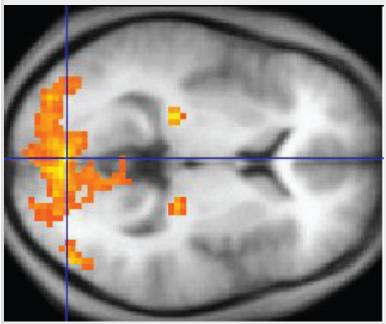
Everyday Connection

How Much of Your Brain Do You Use?

Have you ever heard the claim that humans only use 10 percent of their brains? Maybe you have seen an advertisement on a website saying that there is a secret to unlocking the full potential of your mind—as if there were 90 percent of your brain sitting idle, just waiting for you to use it. If you see an ad like that, don't click. It isn't true.

An easy way to see how much of the brain a person uses is to take measurements of brain activity while performing a task. An example of this kind of measurement is functional magnetic resonance imaging (fMRI), which generates a map of the most active areas and can be generated and presented in three dimensions ([link]). This procedure is different from the standard MRI technique because it is measuring changes in the tissue in time with an experimental condition or event.

fMRI



This fMRI shows activation of the visual cortex in response to visual stimuli. (credit: "Superborsuk"/Wikimedia Commons)

The underlying assumption is that active nervous tissue will have greater blood flow. By having the subject perform a visual task, activity all over the brain can be measured. Consider this possible experiment: the subject is told to look at a screen with a black dot in the middle (a fixation point). A photograph of a face is projected on the screen away from the center. The subject has to look at the photograph and decipher what it is. The subject has been instructed to push a button if the photograph is of someone they recognize. The photograph might be of a celebrity, so the

subject would press the button, or it might be of a random person unknown to the subject, so the subject would not press the button. In this task, visual sensory areas would be active, integrating areas would be active, motor areas responsible for moving the eyes would be active, and motor areas for pressing the button with a finger would be active. Those areas are distributed all around the brain and the fMRI images would show activity in more than just 10 percent of the brain (some evidence suggests that about 80 percent of the brain is using energy—based on blood flow to the tissue—during well-defined tasks similar to the one suggested above). This task does not even include all of the functions the brain performs. There is no language response, the body is mostly lying still in the MRI machine, and it does not consider the autonomic functions that would be ongoing in the background.

Chapter Review

The nervous system can be separated into divisions on the basis of anatomy and physiology. The anatomical divisions are the central and peripheral nervous systems. The CNS is the brain and spinal cord. The PNS is everything else. Functionally, the nervous system can be divided into those regions that are responsible for sensation, those that are responsible for integration, and those that are responsible for generating responses. All of these functional areas are found in both the central and peripheral anatomy.

Considering the anatomical regions of the nervous system, there are specific names for the structures within each division. A localized collection of neuron cell bodies is referred to as a nucleus in the CNS and as a ganglion in the PNS. A bundle of axons is referred to as a tract in the CNS and as a nerve in the PNS. Whereas nuclei and ganglia are specifically in the central or peripheral divisions, axons can cross the boundary between the two. A single axon can be part of a nerve and a tract. The name for that specific structure depends on its location.

Nervous tissue can also be described as gray matter and white matter on the basis of its appearance in unstained tissue. These descriptions are more often used in the CNS. Gray matter is where nuclei are found and white

matter is where tracts and oligodendrocytes are found. In the PNS, ganglia are basically gray matter and nerves are white matter and schwann cells. Regardless of whether we are speaking of the CNS or PNS, the function of white matter is to propagate action potentials while the gray matter is important in synaptic transmission and neural integration.

The nervous system can also be divided on the basis of how it controls the body. The somatic nervous system (SNS) is responsible for functions that result in moving skeletal muscles. Any sensory or integrative functions that result in the movement of skeletal muscle would be considered somatic. The autonomic nervous system (ANS) is responsible for functions that affect cardiac or smooth muscle tissue, or that cause glands to produce their secretions. Autonomic functions are distributed between central and peripheral regions of the nervous system. The sensations that lead to autonomic functions can be the same sensations that are part of initiating somatic responses. Somatic and autonomic integrative functions may overlap as well.

A special division of the nervous system is the enteric nervous system, which is responsible for controlling the digestive organs. Parts of the autonomic nervous system overlap with the enteric nervous system. The enteric nervous system is exclusively found in the periphery because it is the nervous tissue in the organs of the digestive system.

Glossary

autonomic nervous system (ANS)

functional division of the nervous system that is responsible for homeostatic reflexes that coordinate control of cardiac and smooth muscle, as well as glandular tissue

axon

single process of the neuron that carries an electrical signal (action potential) away from the cell body toward a target cell

brain

the large organ of the central nervous system composed of white and gray matter, contained within the cranium and continuous with the spinal cord

central nervous system (CNS)

anatomical division of the nervous system located within the cranial and vertebral cavities, namely the brain and spinal cord

dendrite

one of many branchlike processes that extends from the neuron cell body and functions as a contact for incoming signals (synapses) from other neurons or sensory cells

enteric nervous system (ENS)

neural tissue associated with the digestive system that is responsible for nervous control through autonomic connections

ganglion

localized collection of neuron cell bodies in the peripheral nervous system

glial cell

one of the various types of neural tissue cells responsible for maintenance of the tissue, and largely responsible for supporting neurons

gray matter

regions of the nervous system containing cell bodies of neurons with few or no myelinated axons; actually may be more pink or tan in color, but called gray in contrast to white matter

integration

nervous system function that combines sensory perceptions and higher cognitive functions (memories, learning, emotion, etc.) to produce a response

myelin

lipid-rich insulating substance surrounding the axons of many neurons, allowing for faster transmission of electrical signals

nerve

cord-like bundle of axons located in the peripheral nervous system that transmits sensory input and response output to and from the central nervous system

neuron

neural tissue cell that is primarily responsible for generating and propagating electrical signals into, within, and out of the nervous system

nucleus

in the nervous system, a localized collection of neuron cell bodies that are functionally related; a "center" of neural function

peripheral nervous system (PNS)

anatomical division of the nervous system that is largely outside the cranial and vertebral cavities, namely all parts except the brain and spinal cord

process

in cells, an extension of a cell body; in the case of neurons, this includes the axon and dendrites

response

nervous system function that causes a target tissue (muscle or gland) to produce an event as a consequence to stimuli

sensation

nervous system function that receives information from the environment and translates it into the electrical signals of nervous tissue

soma

in neurons, that portion of the cell that contains the nucleus; the cell body, as opposed to the cell processes (axons and dendrites)

somatic nervous system (SNS)

functional division of the nervous system that is concerned with conscious perception, voluntary movement, and skeletal muscle reflexes

spinal cord

organ of the central nervous system found within the vertebral cavity and connected with the periphery through spinal nerves; mediates reflex behaviors

stimulus

an event in the external or internal environment that registers as activity in a sensory neuron

tract

bundle of axons in the central nervous system having the same function and point of origin

white matter

regions of the nervous system containing mostly myelinated axons, making the tissue appear white because of the high lipid content of myelin

OU Human Physiology: Nervous Tissue By the end of this section, you will be able to:

- Describe the basic structure of a neuron
- Identify the different types of neurons on the basis of polarity
- List the glial cells of the CNS and describe their function
- List the glial cells of the PNS and describe their function

Nervous tissue is composed of two types of cells, neurons and glial cells. Neurons are the primary type of cell that most anyone associates with the nervous system. They are responsible for the computation and communication that the nervous system provides. They are electrically active and release chemical signals to target cells. Glial cells, or glia, are known to play a supporting role for nervous tissue. Ongoing research pursues an expanded role that glial cells might play in signaling, but neurons are still considered the basis of this function. Neurons are important, but without glial support they would not be able to perform their function.

Neurons

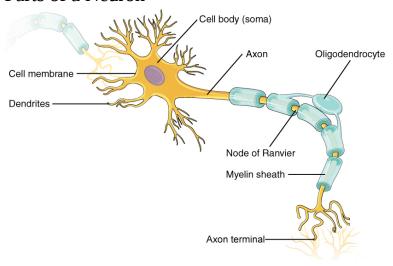
Neurons are the cells considered to be the basis of nervous tissue. They are responsible for the electrical signals that communicate information about sensations, and that produce movements in response to those stimuli, along with inducing thought processes within the brain. An important part of the function of neurons is in their structure, or shape. The three-dimensional shape of these cells makes the immense numbers of connections within the nervous system possible.

Parts of a Neuron

The main part of a neuron is the cell body, which is also known as the soma (soma = "body"). The cell body contains the nucleus and most of the major organelles. But what makes neurons special is that they have many extensions of their cell membranes, which are generally referred to as processes. Neurons are usually described as having one, and only one, axon

—a fiber that emerges from the cell body and projects to target cells. That single axon can branch repeatedly to communicate with many target cells. It is the axon that propagates the nerve impulse, which is communicated to one or more cells. The other processes of the neuron are dendrites, which receive information from other neurons at specialized areas of contact called **synapses**. The dendrites are usually highly branched processes, providing locations for other neurons to communicate with the cell body. Information flows through a neuron from the dendrites, across the cell body, and down the axon and to the axon terminal. This gives the neuron a polarity—meaning that information flows in this one direction. [link] shows the relationship of these parts to one another.

Parts of a Neuron



The major parts of the neuron are labeled on a multipolar neuron from the CNS.

Where the axon emerges from the cell body, there is a special region referred to as the **axon hillock**. This is a tapering of the cell body toward the axon fiber. Within the axon hillock, the cytoplasm changes to a solution of limited components called **axoplasm**. Because the axon hillock represents the beginning of the axon, it is also referred to as the **initial segment**.

Many axons are wrapped by an insulating substance called myelin, which is actually made from glial cells. Myelin acts as insulation much like the plastic or rubber that is used to insulate electrical wires. A key difference between myelin and the insulation on a wire is that there are gaps in the myelin covering of an axon. Each gap is called a **node of Ranvier** and is important to the way that electrical signals travel down the axon. The length of the axon between each gap, which is wrapped in myelin, is referred to as an **axon segment**. At the end of the axon is the **axon terminal**. These terminals are what make the connection with the target cell at the synapse.

Note:



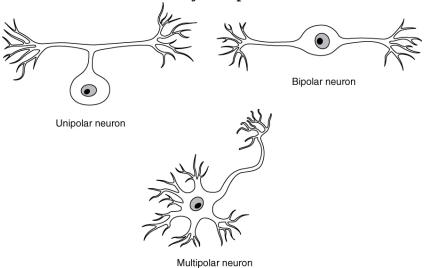
Visit this <u>site</u> to learn about how nervous tissue is composed of neurons and glial cells. Neurons are dynamic cells with the ability to make a vast number of connections, to respond incredibly quickly to stimuli, and to initiate movements on the basis of those stimuli. They are the focus of intense research because failures in physiology can lead to devastating illnesses. Why are neurons only found in animals? Based on what this article says about neuron function, why wouldn't they be helpful for plants or microorganisms?

Types of Neurons

There are many neurons in the nervous system—a number in the trillions. And there are many different types of neurons. They can be classified by many different criteria. The first way to classify them is by the number of processes attached to the cell body. Using the standard model of neurons, one of these processes is the axon, and the rest are dendrites. Because

information flows through the neuron from dendrites or cell bodies toward the axon, these names are based on the neuron's polarity ([link]).

Neuron Classification by Shape



Unipolar cells have one process that includes both the axon and dendrite. Bipolar cells have two processes, the axon and a dendrite. Multipolar cells have more than two processes, the axon and two or more dendrites.

Unipolar cells have only one process emerging from the cell. True unipolar cells are only found in invertebrate animals, so the unipolar cells in humans are more appropriately called "pseudo-unipolar" cells. Invertebrate unipolar cells do not have dendrites. Human unipolar cells have an axon that emerges from the cell body, but it splits so that the axon can extend along a very long distance. At one end of the axon are dendrites, and at the other end, the axon forms synaptic connections with a target. Unipolar cells are exclusively sensory neurons and have two unique characteristics. First, their dendrites are receiving sensory information, sometimes directly from the stimulus itself. Secondly, the cell bodies of unipolar neurons are always found in ganglia. Sensory reception is a peripheral function (those dendrites are in the periphery, perhaps in the skin) so the cell body is in the periphery, though closer to the CNS in a ganglion. The axon projects from the dendrite

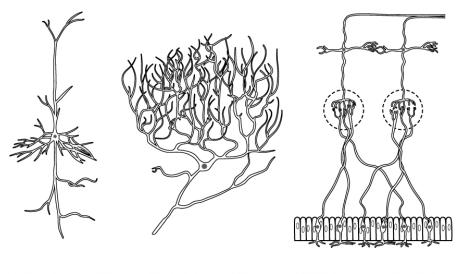
endings, past the cell body in a ganglion, and into the central nervous system.

Bipolar cells have two processes, which extend from each end of the cell body, opposite to each other. One is the axon and one the dendrite. Bipolar cells are not very common. They are found mainly in the olfactory epithelium (where smell stimuli are sensed), and as part of the retina.

Multipolar neurons are all of the neurons that are not unipolar or bipolar. They have one axon and two or more dendrites (usually many more). With the exception of the unipolar sensory ganglion cells, and the two specific bipolar cells mentioned above, all other neurons are multipolar. Some cutting edge research suggests that certain neurons in the CNS do not conform to the standard model of "one, and only one" axon. Some sources describe a fourth type of neuron, called an anaxonic neuron. The name suggests that it has no axon (an- = "without"), but this is not accurate. Anaxonic neurons are very small, and if you look through a microscope at the standard resolution used in histology (approximately 400X to 1000X total magnification), you will not be able to distinguish any process specifically as an axon or a dendrite. Any of those processes can function as an axon depending on the conditions at any given time. Nevertheless, even if they cannot be easily seen, and one specific process is definitively the axon, these neurons have multiple processes and are therefore multipolar.

Neurons can also be classified on the basis of where they are found, who found them, what they do, or even what chemicals they use to communicate with each other. Some neurons referred to in this section on the nervous system are named on the basis of those sorts of classifications ([link]). For example, a multipolar neuron that has a very important role to play in a part of the brain called the cerebellum is known as a Purkinje (commonly pronounced per-KIN-gee) cell. It is named after the anatomist who discovered it (Jan Evangilista Purkinje, 1787–1869).

Other Neuron Classifications



(a) Pyramidal cell of the cerebral cortex

(b) Purkinje cell of the cerebellar cortex

(c) Olfactory cells in the olfactory epithelium and olfactory bulbs

Three examples of neurons that are classified on the basis of other criteria. (a) The pyramidal cell is a multipolar cell with a cell body that is shaped something like a pyramid. (b) The Purkinje cell in the cerebellum was named after the scientist who originally described it. (c) Olfactory neurons are named for the functional group with which they belong.

Glial Cells

Glial cells, or neuroglia or simply glia, are the other type of cell found in nervous tissue. They are considered to be supporting cells, and many functions are directed at helping neurons complete their function for communication. The name glia comes from the Greek word that means "glue," and was coined by the German pathologist Rudolph Virchow, who wrote in 1856: "This connective substance, which is in the brain, the spinal cord, and the special sense nerves, is a kind of glue (neuroglia) in which the nervous elements are planted." Today, research into nervous tissue has shown that there are many deeper roles that these cells play. And research may find much more about them in the future.

There are six types of glial cells. Four of them are found in the CNS and two are found in the PNS. [link] outlines some common characteristics and functions.

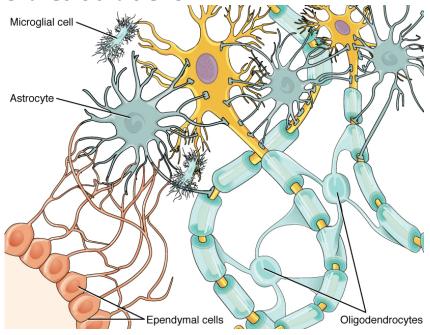
Glial Cell Types by Location and Basic Function		
CNS glia	PNS glia	Basic function
Astrocyte	Satellite cell	Support
Oligodendrocyte	Schwann cell	Insulation, myelination
Microglia	-	Immune surveillance and phagocytosis
Ependymal cell	-	Creating CSF

Glial Cells of the CNS

One cell providing support to neurons of the CNS is the **astrocyte**, so named because it appears to be star-shaped under the microscope (astro-= "star"). Astrocytes have many processes extending from their main cell body (not axons or dendrites like neurons, just cell extensions). Those processes extend to interact with neurons, blood vessels, or the connective tissue covering the CNS that is called the pia mater ([link]). Generally, they are supporting cells for the neurons in the central nervous system. Some ways in which they support neurons in the central nervous system are by maintaining the concentration of chemicals in the extracellular space,

removing excess signaling molecules, reacting to tissue damage, and contributing to the **blood-brain barrier (BBB)**. The blood-brain barrier is a physiological barrier that keeps many substances that circulate in the rest of the body from getting into the central nervous system, restricting what can cross from circulating blood into the CNS. Nutrient molecules, such as glucose or amino acids, can pass through the BBB, but other molecules cannot. This actually causes problems with drug delivery to the CNS. Pharmaceutical companies are challenged to design drugs that can cross the BBB as well as have an effect on the nervous system.

Glial Cells of the CNS



The CNS has astrocytes, oligodendrocytes, microglia, and ependymal cells that support the neurons of the CNS in several ways.

Like a few other parts of the body, the brain has a privileged blood supply. Very little can pass through by diffusion. Most substances that cross the wall of a blood vessel into the CNS must do so through an active transport process. Because of this, only specific types of molecules can enter the CNS. Glucose—the primary energy source—is allowed, as are amino acids. Water and some other small particles, like gases and ions, can enter. But

most everything else cannot, including white blood cells, which are one of the body's main lines of defense. While this barrier protects the CNS from exposure to toxic or pathogenic substances, it also keeps out the cells that could protect the brain and spinal cord from disease and damage. The BBB also makes it harder for pharmaceuticals to be developed that can affect the nervous system. Aside from finding efficacious substances, the means of delivery is also crucial.

Also found in CNS tissue is the **oligodendrocyte**, sometimes called just "oligo," which is the glial cell type that insulates axons in the CNS. The name means "cell of a few branches" (oligo- = "few"; dendro- = "branches"; -cyte = "cell"). There are a few processes that extend from the cell body. Each one reaches out and surrounds an axon to insulate it in myelin. One oligodendrocyte will provide the myelin for multiple axon segments, either for the same axon or for separate axons. The function of myelin will be discussed below.

Microglia are, as the name implies, smaller than most of the other glial cells. Ongoing research into these cells, although not entirely conclusive, suggests that they may originate as white blood cells, called macrophages, that become part of the CNS during early development. While their origin is not conclusively determined, their function is related to what macrophages do in the rest of the body. When macrophages encounter diseased or damaged cells in the rest of the body, they ingest and digest those cells or the pathogens that cause disease. Microglia are the cells in the CNS that can do this in normal, healthy tissue, and they are therefore also referred to as CNS-resident macrophages.

The **ependymal cell** is a glial cell that filters blood to make **cerebrospinal fluid (CSF)**, the fluid that circulates through the CNS. Because of the privileged blood supply inherent in the BBB, the extracellular space in nervous tissue does not easily exchange components with the blood. Ependymal cells line each **ventricle**, one of four central cavities that are remnants of the hollow center of the neural tube formed during the embryonic development of the brain. The **choroid plexus** is a specialized structure in the ventricles where ependymal cells come in contact with blood vessels and filter and absorb components of the blood to produce

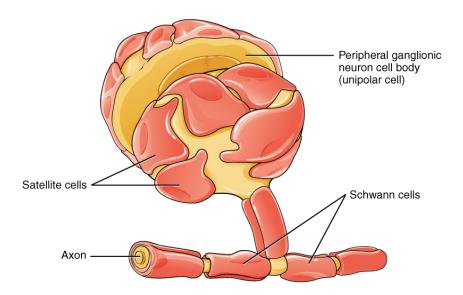
cerebrospinal fluid. Because of this, ependymal cells can be considered a component of the BBB, or a place where the BBB breaks down. These glial cells appear similar to epithelial cells, making a single layer of cells with little intracellular space and tight connections between adjacent cells. They also have cilia on their apical surface to help move the CSF through the ventricular space. The relationship of these glial cells to the structure of the CNS is seen in [link].

Glial Cells of the PNS

One of the two types of glial cells found in the PNS is the **satellite cell**. Satellite cells are found in sensory and autonomic ganglia, where they surround the cell bodies of neurons. This accounts for the name, based on their appearance under the microscope. They provide support, performing similar functions in the periphery as astrocytes do in the CNS—except, of course, for establishing the BBB.

The second type of glial cell is the **Schwann cell**, which insulate axons with myelin in the periphery. Schwann cells are different than oligodendrocytes, in that a Schwann cell wraps around a portion of only one axon segment and no others. Oligodendrocytes have processes that reach out to multiple axon segments, whereas the entire Schwann cell surrounds just one axon segment. The nucleus and cytoplasm of the Schwann cell are on the edge of the myelin sheath. The relationship of these two types of glial cells to ganglia and nerves in the PNS is seen in [link].

Glial Cells of the PNS



The PNS has satellite cells and Schwann cells.

Myelin

The insulation for axons in the nervous system is provided by glial cells, oligodendrocytes in the CNS, and Schwann cells in the PNS. Whereas the manner in which either cell is associated with the axon segment, or segments, that it insulates is different, the means of myelinating an axon segment is mostly the same in the two situations. Myelin is a lipid-rich sheath that surrounds the axon and by doing so creates a **myelin sheath** that facilitates the transmission of electrical signals along the axon. The lipids are essentially the phospholipids of the glial cell membrane. Myelin, however, is more than just the membrane of the glial cell. It also includes important proteins that are integral to that membrane. Some of the proteins help to hold the layers of the glial cell membrane closely together.

The appearance of the myelin sheath can be thought of as similar to the pastry wrapped around a hot dog for "pigs in a blanket" or a similar food. The glial cell is wrapped around the axon several times with little to no cytoplasm between the glial cell layers. For oligodendrocytes, the rest of the cell is separate from the myelin sheath as a cell process extends back

toward the cell body. A few other processes provide the same insulation for other axon segments in the area. For Schwann cells, the outermost layer of the cell membrane contains cytoplasm and the nucleus of the cell as a bulge on one side of the myelin sheath. During development, the glial cell is loosely or incompletely wrapped around the axon ([link]a). The edges of this loose enclosure extend toward each other, and one end tucks under the other. The inner edge wraps around the axon, creating several layers, and the other edge closes around the outside so that the axon is completely enclosed.

Note:

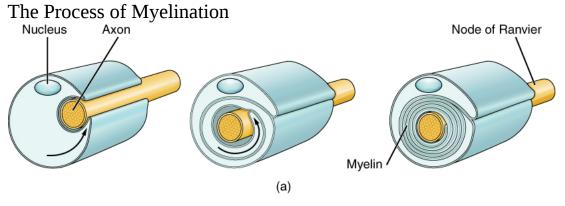


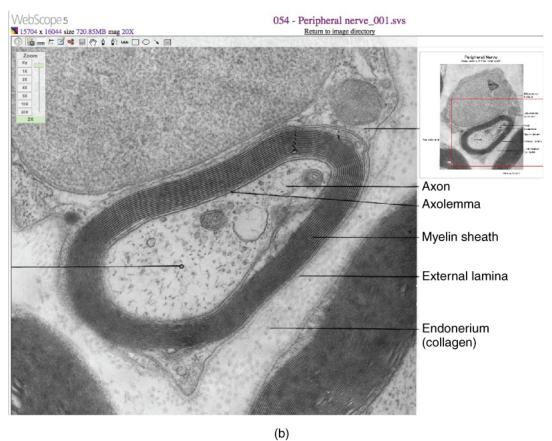
View the University of Michigan WebScope at http://virtualslides.med.umich.edu/Histology/EMsmallCharts/3%20Image/20Scope%20finals/054%20-

<u>%20Peripheral%20nerve 001.svs/view.apml?listview=1&</u> to see an electron micrograph of a cross-section of a myelinated nerve fiber. The axon contains microtubules and neurofilaments that are bounded by a plasma membrane known as the axolemma. Outside the plasma membrane of the axon is the myelin sheath, which is composed of the tightly wrapped plasma membrane of a Schwann cell. What aspects of the cells in this image react with the stain to make them a deep, dark, black color, such as the multiple layers that are the myelin sheath?

Myelin sheaths can extend for one or two millimeters, depending on the diameter of the axon. Axon diameters can be as small as 1 to 20 micrometers. Because a micrometer is 1/1000 of a millimeter, this means that the length of a myelin sheath can be 100–1000 times the diameter of

the axon. [link], [link], and [link] show the myelin sheath surrounding an axon segment, but are not to scale. If the myelin sheath were drawn to scale, the neuron would have to be immense—possibly covering an entire wall of the room in which you are sitting.





Myelinating glia wrap several layers of cell membrane around the cell membrane of an axon segment. A single Schwann cell insulates a segment of a peripheral nerve, whereas in the CNS, an oligodendrocyte may provide insulation for a few separate

axon segments. EM × 1,460,000. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:

Disorders of the...

Nervous Tissue

Several diseases can result from the demyelination of axons. The causes of these diseases are not the same; some have genetic causes, some are caused by pathogens, and others are the result of autoimmune disorders. Though the causes are varied, the results are largely similar. The myelin insulation of axons is compromised, making electrical signaling slower. Multiple sclerosis (MS) is one such disease. It is an example of an autoimmune disease. The antibodies produced by lymphocytes (a type of white blood cell) mark myelin as something that should not be in the body. This causes inflammation and the destruction of the myelin in the central nervous system. As the insulation around the axons is destroyed by the disease, scarring becomes obvious. This is where the name of the disease comes from; sclerosis means hardening of tissue, which is what a scar is. Multiple scars are found in the white matter of the brain and spinal cord. The symptoms of MS include both somatic and autonomic deficits. Control of the musculature is compromised, as is control of organs such as the bladder.

Guillain-Barré (pronounced gee-YAN bah-RAY) syndrome is an example of a demyelinating disease of the peripheral nervous system. It is also the result of an autoimmune reaction, but the inflammation is in peripheral nerves. Sensory symptoms or motor deficits are common, and autonomic failures can lead to changes in the heart rhythm or a drop in blood pressure, especially when standing, which causes dizziness.

Chapter Review

Nervous tissue contains two major cell types, neurons and glial cells. Neurons are the cells responsible for communication through electrical signals. Glial cells are supporting cells, maintaining the environment around the neurons.

Neurons are polarized cells, based on the flow of electrical signals along their membrane. Signals are received at the dendrites, are passed along the cell body, and propagate along the axon towards the target, which may be another neuron, muscle tissue, or a gland. Many axons are insulated by a lipid-rich substance called myelin. Specific types of glial cells provide this insulation.

Several types of glial cells are found in the nervous system, and they can be categorized by the anatomical division in which they are found. In the CNS, astrocytes, oligodendrocytes, microglia, and ependymal cells are found. Astrocytes are important for maintaining the chemical environment around the neuron and are crucial for regulating the blood-brain barrier. Oligodendrocytes are the myelinating glia in the CNS. Microglia act as phagocytes and play a role in immune surveillance. Ependymal cells are responsible for filtering the blood to produce cerebrospinal fluid, which is a circulatory fluid that performs some of the functions of blood in the brain and spinal cord because of the BBB. In the PNS, satellite cells are supporting cells for the neurons, and Schwann cells insulate peripheral axons.

Glossary

astrocyte

glial cell type of the CNS that provides support for neurons and maintains the blood-brain barrier

axon hillock

tapering of the neuron cell body that gives rise to the axon

axon segment

single stretch of the axon insulated by myelin and bounded by nodes of Ranvier at either end (except for the first, which is after the initial segment, and the last, which is followed by the axon terminal)

axon terminal

end of the axon, where there are usually several branches extending toward the target cell

axoplasm

cytoplasm of an axon, which is different in composition than the cytoplasm of the neuronal cell body

bipolar

shape of a neuron with two processes extending from the neuron cell body—the axon and one dendrite

blood-brain barrier (BBB)

physiological barrier between the circulatory system and the central nervous system that establishes a privileged blood supply, restricting the flow of substances into the CNS

cerebrospinal fluid (CSF)

circulatory medium within the CNS that is produced by ependymal cells in the choroid plexus filtering the blood

choroid plexus

specialized structure containing ependymal cells that line blood capillaries and filter blood to produce CSF in the four ventricles of the brain

ependymal cell

glial cell type in the CNS responsible for producing cerebrospinal fluid

initial segment

first part of the axon as it emerges from the axon hillock, where the electrical signals known as action potentials are generated

microglia

glial cell type in the CNS that serves as the resident component of the immune system

multipolar

shape of a neuron that has multiple processes—the axon and two or more dendrites

myelin sheath

lipid-rich layer of insulation that surrounds an axon, formed by oligodendrocytes in the CNS and Schwann cells in the PNS; facilitates the transmission of electrical signals

node of Ranvier

gap between two myelinated regions of an axon, allowing for strengthening of the electrical signal as it propagates down the axon

oligodendrocyte

glial cell type in the CNS that provides the myelin insulation for axons in tracts

satellite cell

glial cell type in the PNS that provides support for neurons in the ganglia

Schwann cell

glial cell type in the PNS that provides the myelin insulation for axons in nerves

synapse

narrow junction across which a chemical signal passes from neuron to the next, initiating a new electrical signal in the target cell

unipolar

shape of a neuron which has only one process that includes both the axon and dendrite

ventricle

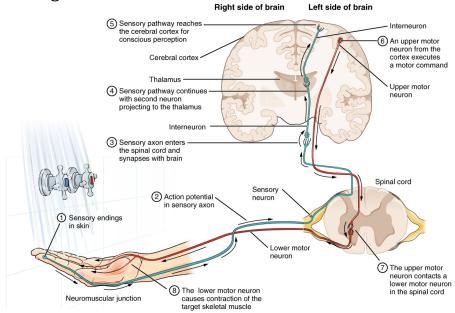
central cavity within the brain where CSF is produced and circulates

OU Human Physiology: The Function of Nervous Tissue By the end of this section, you will be able to:

- Distinguish the major functions of the nervous system: sensation (stimuli), integration, and response
- List the sequence of events in a simple sensory receptor—motor response pathway.
- Describe the function of each structure of a neuron

Having looked at the components of nervous tissue, and the basic anatomy of the nervous system, next comes an understanding of how nervous tissue is capable of communicating within the nervous system. Before getting to the nuts and bolts of how this works, an illustration of how the components come together will be helpful. An example is summarized in [link].

Testing the Water



(1) The sensory neuron has endings in the skin that sense a stimulus such as water temperature. The strength of the signal that starts here is dependent on the strength of the stimulus. (2) The graded potential from the sensory endings, if strong enough, will initiate an action potential at the initial segment of the axon (which is immediately

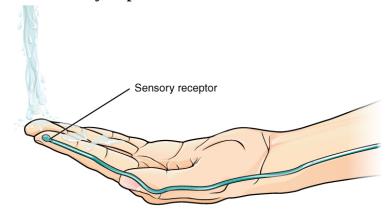
adjacent to the sensory endings in the skin). (3) The axon of the peripheral sensory neuron enters the spinal cord and contacts another neuron in the gray matter. The contact is a synapse where another graded potential is caused by the release of a chemical signal from the axon terminals. (4) An action potential is initiated at the initial segment of this neuron and travels up the sensory pathway to a region of the brain called the thalamus. Another synapse passes the information along to the next neuron. (5) The sensory pathway ends when the signal reaches the cerebral cortex. (6) After integration with neurons in other parts of the cerebral cortex, a motor command is sent from the precentral gyrus of the frontal cortex. (7) The upper motor neuron sends an action potential down to the spinal cord. The target of the upper motor neuron is the dendrites of the lower motor neuron in the gray matter of the spinal cord. (8) The axon of the lower motor neuron emerges from the spinal cord in a nerve and connects to a muscle through a neuromuscular junction to cause contraction of the target muscle.

Imagine you are about to take a shower in the morning before going to school. You have turned on the faucet to start the water as you prepare to get in the shower. After a few minutes, you expect the water to be a temperature that will be comfortable to enter. So you put your hand out into the spray of water. What happens next depends on how your nervous system interacts with the stimulus of the water temperature and what you do in response to that stimulus.

Found in the skin of your fingers or toes is a type of sensory receptor that is sensitive to temperature, called a **thermoreceptor**. When you place your hand under the shower ([link]), the cell membrane of the thermoreceptors

changes its electrical state (voltage). The amount of change is dependent on the strength of the stimulus (how hot the water is). This is called a **graded potential**. This graded potential will be generated at the dendrite or cell body of the neuron and travel toward the axon hillock. If the stimulus is strong enough, the voltage of the cell membrane will change enough to generate an electrical signal that spreads down the axon and into the axon terminal. The voltage at which such a signal is generated is called the **threshold** (-55mV), and the resulting electrical signal is called an **action potential**. In this example, the action potential travels—a process known as **propagation**—along the axon from the axon hillock to the axon terminals. When this signal reaches the axon terminal, it causes the release of a signaling molecule called a **neurotransmitter**.

The Sensory Input



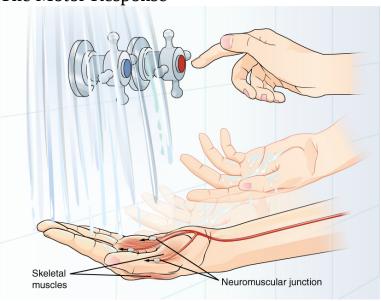
Receptors in the skin sense the temperature of the water.

The neurotransmitter diffuses across the short distance of the synapse and binds to a receptor protein of the target neuron. When the molecular signal binds to the receptor, the cell membrane of the target neuron changes its electrical state and a new graded potential begins. If that graded potential is strong enough to reach threshold, the second neuron generates an action potential at its axon hillock. The target of this neuron is another neuron in the **thalamus** of the brain, the part of the CNS that acts as a relay for sensory information. At another synapse, neurotransmitter is released and binds to its receptor. The thalamus then sends the sensory information to the

cerebral cortex, the outermost layer of gray matter in the brain, where conscious perception of that water temperature begins.

Within the cerebral cortex, information is processed among many neurons, integrating the stimulus of the water temperature with other sensory stimuli, with your emotional state (you just aren't ready to wake up; the bed is calling to you), memories (perhaps of the lab notes you have to study before a quiz). Finally, a plan is developed about what to do, whether that is to turn the temperature up, turn the whole shower off and go back to bed, or step into the shower. To do any of these things, the cerebral cortex has to send a command out to your body to move muscles ([link]).

The Motor Response



On the basis of the sensory input and the integration in the CNS, a motor response is formulated and executed.

A region of the cortex is specialized for sending signals down to the spinal cord for movement. The **upper motor neuron** is in this region, called the **precentral gyrus of the frontal cortex**, which has an axon that extends all the way down the spinal cord. At the level of the spinal cord at which this axon makes a synapse, a graded potential occurs in the cell membrane of a

lower motor neuron. This second motor neuron is responsible for causing muscle fibers to contract when an action potential travels along the motor neuron axon into the periphery. The axon terminates on muscle fibers at the neuromuscular junction. Acetylcholine is released at this specialized synapse, which causes the muscle action potential to begin, following a large potential known as an end plate potential. When the lower motor neuron excites the muscle fiber, it contracts. All of this occurs in a fraction of a second, but this story is the basis of how the nervous system functions. We will return to the events occurring at the neuromuscular junction later. At this point you have an idea as to where electrical signals go once generated via a stimulus and that a response occurs. But what is that electrical signal that travels down the axon and into the axon terminal? We will explore action potentials in the next section.

Note:

Career Connections

Neurophysiologist

Understanding how the nervous system works could be a driving force in your career. Studying neurophysiology is a very rewarding path to follow. It means that there is a lot of work to do, but the rewards are worth the effort.

The career path of a research scientist can be straightforward: college, graduate school, postdoctoral research, academic research position at a university. A Bachelor's degree in science will get you started, and for neurophysiology that might be in biology, psychology, computer science, engineering, or neuroscience. But the real specialization comes in graduate school. There are many different programs out there to study the nervous system, not just neuroscience itself. Most graduate programs are doctoral, meaning that a Master's degree is not part of the work. These are usually considered five-year programs, with the first two years dedicated to course work and finding a research mentor, and the last three years dedicated to finding a research topic and pursuing that with a near single-mindedness. The research will usually result in a few publications in scientific journals, which will make up the bulk of a doctoral dissertation. After graduating with a Ph.D., researchers will go on to find specialized work called a

postdoctoral fellowship within established labs. In this position, a researcher starts to establish their own research career with the hopes of finding an academic position at a research university.

Other options are available if you are interested in how the nervous system works. Especially for neurophysiology, a medical degree might be more suitable so you can learn about the clinical applications of neurophysiology and possibly work with human subjects. An academic career is not a necessity. Biotechnology firms are eager to find motivated scientists ready to tackle the tough questions about how the nervous system works so that therapeutic chemicals can be tested on some of the most challenging disorders such as Alzheimer's disease or Parkinson's disease, or spinal cord injury.

Others with a medical degree and a specialization in neuroscience go on to work directly with patients, diagnosing and treating mental disorders. You can do this as a psychiatrist, a neuropsychologist, a neuroscience nurse, or a neurodiagnostic technician, among other possible career paths.

Chapter Review

Sensation starts with the activation of a sensory ending, such as the thermoreceptor in the skin sensing the temperature of the water. The sensory endings in the skin initiate an electrical signal that travels along the sensory axon within a nerve into the spinal cord, where it synapses with a neuron in the gray matter of the spinal cord. The temperature information represented in that electrical signal is passed to the next neuron by a chemical signal that diffuses across the small gap of the synapse and initiates a new electrical signal in the target cell. That signal travels through the sensory pathway to the brain, passing through the thalamus, where conscious perception of the water temperature is made possible by the cerebral cortex. Following integration of that information with other cognitive processes and sensory information, the brain sends a command back down to the spinal cord to initiate a motor response by controlling a skeletal muscle. The motor pathway is composed of two cells, the upper motor neuron and the lower motor neuron. The upper motor neuron has its cell body in the cerebral cortex and synapses on a cell in the gray matter of

the spinal cord. The lower motor neuron is that cell in the gray matter of the spinal cord and its axon extends into the periphery where it synapses with a skeletal muscle in a neuromuscular junction.

Glossary

action potential

change in voltage of a cell membrane in response to a stimulus that results in transmission of an electrical signal; unique to neurons and muscle fibers

cerebral cortex

outermost layer of gray matter in the brain, where conscious perception takes place

graded potential

change in the membrane potential that varies in size, depending on the size of the stimulus that elicits it

lower motor neuron

second neuron in the motor command pathway that is directly connected to the skeletal muscle

neurotransmitter

chemical signal that is released from the synaptic end bulb of a neuron to cause a change in the target cell

precentral gyrus of the frontal cortex

region of the cerebral cortex responsible for generating motor commands, where the upper motor neuron cell body is located

propagation

movement of an action potential along the length of an axon

thalamus

region of the central nervous system that acts as a relay for sensory pathways

thermoreceptor

type of sensory receptor capable of transducing temperature stimuli into neural action potentials

threshold

membrane voltage at which an action potential is initiated

upper motor neuron

first neuron in the motor command pathway with its cell body in the cerebral cortex that synapses on the lower motor neuron in the spinal cord

OU Human Physiology: The Action Potential By the end of this section, you will be able to:

- Identify the types of gated channels
- Discuss the function of each type of gated channel
- Describe the components of the membrane that establish the resting membrane potential
- Describe the changes that occur to the membrane that result in the action potential
- Compare and contrast the configuration of the voltage gated sodium and potassium channels
- Explain why resting membrane potential is negative
- Describe how the Na⁺/K⁺ pump maintains the resting membrane potential and the leak channels set the resting membrane potential
- Describe each phase of the action potential including configuration of the voltage-gated sodium and potassium channels and ion permeabilities
- Compare and contrast refractory periods

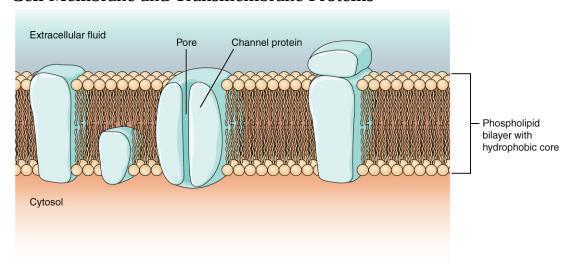
The functions of the nervous system—sensation, integration, and response—depend on the functions of the neurons underlying these pathways. To understand how neurons are able to communicate, it is necessary to describe the role of an **excitable membrane** in generating these signals. The basis of this communication is the action potential, which demonstrates how changes in the membrane can constitute a signal. Looking at the way these signals work in more variable circumstances involves a look at graded potentials, which will be covered in the next section.

Electrically Active Cell Membranes

As you learned in the chapter on cells, the cell membrane is primarily responsible for regulating what can cross the membrane and what stays on only one side. The cell membrane is a phospholipid bilayer, so only substances that can pass directly through the hydrophobic core can diffuse through unaided. Charged particles, which are hydrophilic by definition, cannot pass through the cell membrane without assistance ([link]). Transmembrane proteins, specifically channel proteins, make this possible.

Several channels, as well as specialized energy dependent "ion-pumps," are necessary to generate a transmembrane potential and to generate an action potential. Of special interest is the carrier protein referred to as the sodium/potassium pump that moves sodium ions (Na^+) out of a cell and potassium ions (K^+) into a cell, thus maintaining ion concentration on both sides of the cell membrane.

Cell Membrane and Transmembrane Proteins



The cell membrane is composed of a phospholipid bilayer and has many transmembrane proteins, including different types of channel proteins that serve as ion channels.

The sodium/potassium pump requires energy in the form of adenosine triphosphate (ATP), so it is also referred to as an ATPase. As was explained in the cell chapter, the concentration of Na^+ is higher outside the cell than inside, and the concentration of K^+ is higher inside the cell than outside. That means that this pump is moving the ions against the concentration gradients for sodium and potassium, which is why it requires energy. In fact, the pump basically maintains those concentration gradients.

Ion channels are pores that allow specific charged particles to cross the membrane in response to an existing gradient. Remember channels are a transmembrane protein that exhibit specificity.

Ion channels do not always freely allow ions to diffuse across the membrane. They are opened by certain events, meaning the channels are **gated**. Channels can be categorized is on the basis of how they are gated. Although these classes of ion channels are found primarily in cells of nervous or muscular tissue, they also can be found in cells of epithelial and connective tissues.

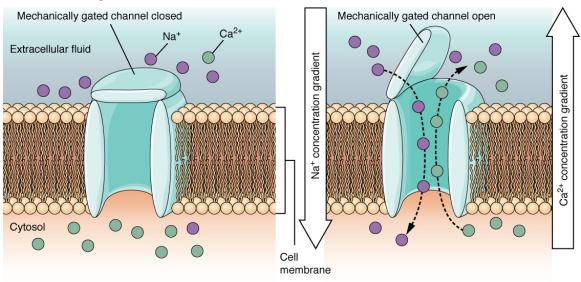
A **ligand-gated channel** opens because a signaling molecule, a ligand, binds to the extracellular region of the channel ([<u>link</u>]).

Ligand-Gated Channels A neurotransmitter. Neurotransmitter Neurotransmitter the ligand, is required attaches to receptor receptor site to open the ion channel Channel closed Extracellular fluid Na⁺ and Ca²⁺ concentration gradient ACh Ca²⁺ concentration gradient Ť Cell membrane Cytosol Chemical stimulus lons move in response to gradient opens the channel

When the ligand, in this case the neurotransmitter acetylcholine, binds to a specific location on the extracellular surface of the channel protein, the pore opens to allow select ions through. The ions, in this case, are cations of sodium, calcium, and potassium.

A **mechanically gated channel** opens because of a physical distortion of the cell membrane. Many channels associated with the sense of touch (somatosensation) are mechanically gated. For example, as pressure is applied to the skin, these channels open and allow ions to enter the cell. Similar to this type of channel would be the channel that opens on the basis of temperature changes, as in testing the water in the shower ([link]).

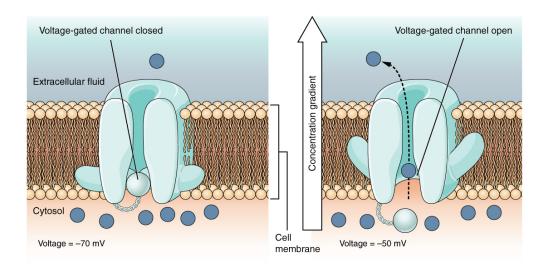
Mechanically Gated Channels



When a mechanical change occurs in the surrounding tissue, such as pressure or touch, the channel is physically opened. Thermoreceptors work on a similar principle. When the local tissue temperature changes, the protein reacts by physically opening the channel.

A **voltage-gated channel** is a channel that responds to changes in the electrical properties of the membrane in which it is embedded. Normally, the inner portion of the membrane is at a negative voltage. When that voltage becomes less negative, the channel begins to allow ions to cross the membrane ([link]).

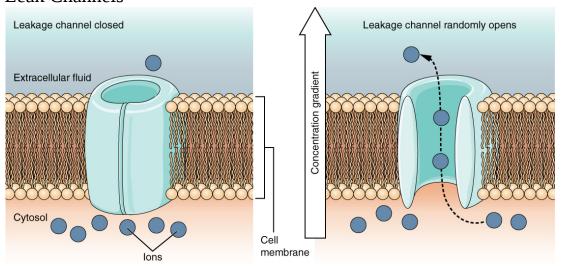
Voltage-Gated Channels



Voltage-gated channels open when the transmembrane voltage changes around them.

A **leak channel** is randomly gated, meaning that it opens and closes at random, hence the reference to leaking. There is no actual event that opens the channel; instead, it has an intrinsic rate of switching between the open and closed states. Leakage channels contribute to the resting transmembrane voltage of the excitable membrane ([link]). For our purposes, we will assume that leak channels are always open unless otherwise discussed.

Leak Channels

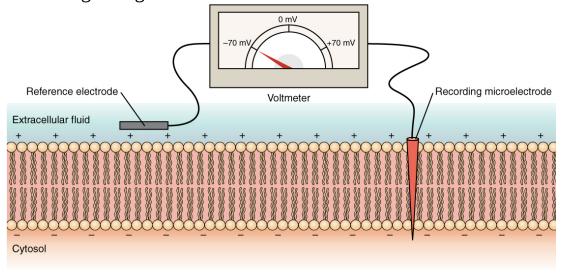


In certain situations, ions need to move across the membrane randomly. The particular electrical properties of certain cells are modified by the presence of this type of channel.

The Membrane Potential

The electrical state of the cell membrane can have several variations. These are all variations in the **membrane potential**. A potential is a distribution of charge across the cell membrane, measured in millivolts (mV). The standard is to compare the inside of the cell relative to the outside, so the membrane potential is a value representing the charge on the intracellular side of the membrane based on the outside being zero, relatively speaking ([link]).

Measuring Charge across a Membrane with a Voltmeter



A recording electrode is inserted into the cell and a reference electrode is outside the cell. By comparing the charge measured by these two electrodes, the transmembrane voltage is determined. It is conventional to express that value for the cytosol relative to the outside.

The concentration of ions in extracellular and intracellular fluids is largely balanced, with a net neutral charge. However, a slight difference in charge occurs right at the membrane surface, both internally and externally. It is the difference in this very limited region that has all the power in neurons (and muscle cells) to generate electrical signals, including action potentials.

Before these electrical signals can be described, the resting state of the membrane must be explained. When the cell is at rest (in other words it is not responding to a stimulus), and the ion channels are closed (except for leak channels), ions are distributed across the membrane in a very predictable way. The concentration of Na⁺ outside the cell is 10 times greater than the concentration inside. Also, the concentration of K⁺ inside the cell is greater than outside. The cytosol contains a high concentration of anions, in the form of phosphate ions and negatively charged proteins that are impermeable. Large anions are a component of the inner cell membrane, including specialized phospholipids and proteins associated with the inner leaflet of the membrane (leaflet is a term used for one side of the lipid bilayer membrane). The negative charge is localized in the large anions.

With the ions distributed across the membrane at these concentrations, the difference in charge is measured at -70 mV, the value described as the **resting membrane potential**. The exact value measured for the resting membrane potential varies between cells, but -70 mV is most commonly used as this value. This voltage would actually be much lower except for the contributions of some important proteins in the membrane. Leak channels allow Na⁺ to slowly move into the cell or K⁺ to slowly move out, and the Na⁺/K⁺ pump restores them. This may appear to be a waste of energy, but each has a role in maintaining the membrane potential.

The Action Potential

Resting membrane potential describes the steady state of the cell, which is a dynamic process that is balanced by ion leakage and ion pumping. Without any outside influence, it will not change. To get an electrical signal started, the membrane potential has to change.

This starts with a channel opening for Na⁺ in the membrane. Because the concentration of Na⁺ is higher outside the cell than inside the cell by a factor of 10, ions will rush into the cell that are driven by a net electrochemical gradient. Because sodium is a positively charged ion, it will change the relative voltage immediately inside the cell relative to immediately outside. The resting potential is the state of the membrane at a voltage of -70 mV, so the sodium cation entering the cell will cause it to become less negative. This is known as **depolarization**, meaning the membrane potential moves toward zero.

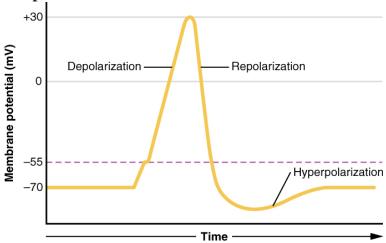
The concentration gradient for Na ⁺ is so strong that it will continue to enter the cell even after the membrane potential has become zero, so that the voltage immediately around the channel begins to become positive and reaches +30 mV. The membrane potential will then become more negative toward the resting voltage during repolarization. Repolarization is due to the efflux of K ⁺ions along an electrochemical gradient via voltage-gated K ⁺ channels.

Repolarization returns the membrane potential to the -70 mV value that indicates the resting potential, but it actually overshoots that value. Potassium ions nearly reach equilibrium when the membrane voltage is below -70 mV, so a period of hyperpolarization occurs while the K^+ channels are open. Those K^+ channels are slightly delayed in closing, accounting for this short overshoot.

What has been described here is the action potential, which is presented as a graph of voltage over time in [link]. It is the electrical signal that nervous tissue generates for communication. The change in the membrane voltage from -70 mV at rest to +30 mV at the end of depolarization is a 100-mV change. That can also be written as a 0.1-V change. To put that value in perspective, think about a battery. An AA battery that you might find in a television remote has a voltage of 1.5 V, or a 9-V battery (the rectangular battery with two posts on one end) is, obviously, 9 V. The change seen in the action potential is one or two orders of magnitude less than the charge in these batteries. In fact, the membrane potential can be described as a battery. A charge is stored across the membrane that can be released under

the correct conditions. A battery in your remote has stored a charge that is "released" when you push a button.

Graph of Action Potential



Plotting voltage measured across the cell membrane against time, the action potential begins with depolarization, followed by repolarization, which goes past the resting potential into hyperpolarization, and finally the membrane returns to rest.

Note:



What happens across the membrane of an electrically active cell is a dynamic process that is hard to visualize with static images or through text descriptions. View this <u>animation</u> to learn more about this process. What is

the difference between the driving force for Na⁺ and K⁺? And what is similar about the movement of these two ions?

The question is, now, what initiates the action potential? The description above conveniently glosses over that point. But it is vital to understanding what is happening. The membrane potential will stay at the resting voltage until something changes. The description above just says that a Na⁺ channel opens. Now, to say "a channel opens" does not mean that one individual transmembrane protein changes. Instead, it means that one kind of channel opens. There are a few different types of channels that allow Na⁺ to cross the membrane. A ligand-gated Na⁺ channel will open when a neurotransmitter binds to it and a mechanically gated Na⁺ channel will open when a physical stimulus affects a sensory receptor (like pressure applied to the skin compresses a touch receptor). Whether it is a neurotransmitter binding to its receptor protein or a sensory stimulus activating a sensory receptor cell, some stimulus gets the process started. Sodium starts to enter the cell and the membrane becomes less negative.

The ligand-gated Na⁺ channels that start depolarizing the membrane because of a stimulus help the cell to depolarize from -70 mV to -55 mV. Negative 55 mV is known as the threshold. Once the membrane reaches that voltage an action potential will occur. Any depolarization that does not change the membrane potential to -55 mV or higher will not reach threshold and thus will not result in an action potential.

Because of the threshold, the action potential can be likened to a digital event—it either happens or it does not. If the threshold is not reached, then no action potential occurs. If depolarization reaches -55 mV, then the action potential continues and runs all the way to +30 mV, at which K⁺ causes repolarization, including the hyperpolarizing overshoot. Also, those changes are the same for every action potential, which means that once the threshold is reached, the exact same thing happens. A stronger stimulus, which might depolarize the membrane well past threshold, will not make a "bigger" action potential. Action potentials are "all or none." Either the membrane reaches the threshold and everything occurs as described above, or the membrane does not reach the threshold and nothing else happens. All

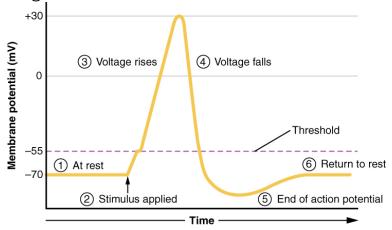
action potentials peak at the same voltage (+30 mV), so one action potential is not bigger than another. Stronger stimuli will initiate multiple action potentials more quickly, but the individual signals are not bigger. Thus, for example, you will not feel a greater sensation of pain, or have a stronger muscle contraction, because of the size of the action potential because they are not different sizes.

The depolarization and repolarization of an action potential are dependent on two types of channels, the voltage-gated Na⁺ channel and the voltage-gated K⁺ channel. The voltage-gated Na⁺ channel actually has two gates. One is the **activation gate**, which opens when the membrane potential crosses -55 mV. The other gate is the **inactivation gate**, which closes after a specific period of time—on the order of a fraction of a millisecond of the activation opening. When a cell is at rest, the activation gate is closed and the inactivation gate is open. This is called the "closed but capable of opening configuration." When the threshold is reached, the activation gate opens, allowing Na⁺ to rush into the cell. The voltage-gated Na+ channels are now in the "open" configuration as both activation and inactivation gates are open. Remember, the opening of the activation gate will trigger the slow closing of the inactivation gates. When the inactivation gate is finally closed and the activation gate is still open, the voltage-gated Na+ channel is now in the "closed and incapable of opening" configuration.

The voltage-gated K⁺ channel has only one gate, which is sensitive to a membrane voltage of -50 mV. However, it does not open as quickly as the voltage-gated Na⁺ channel does. It might take a fraction of a millisecond for the channel to open once that voltage has been reached. The timing of this coincides with the Na⁺ channels are being inactivated. As the membrane potential repolarizes and the voltage passes -70 mV again, the channel closes—again, with a little delay. Potassium continues to leave the cell for a short while and the membrane potential becomes more negative. The voltage-gated K+ channels begin to close, but since they are slow this results in the hyperpolarizing. Once the channels are closed, the membrane can return to the resting membrane potential because of the ongoing activity of the leak channels and the Na⁺/K⁺ pump.

All of this takes place within approximately 2 milliseconds ([link]). While an action potential is in progress, the neuron is in the **refractory period**. There are two phases of the refractory period: the **absolute refractory** period and the **relative refractory period**. During the absolute phase, another action potential will not start. This is because of the inactivation gate of the voltage-gated Na⁺ channel. Once that channel is back to its resting conformation (less than -55 mV), a new action potential could be started, but only by a stronger stimulus than the one that initiated the current action potential. This is because of the flow of K⁺ out of the cell. Because that ion is rushing out, any Na+ that tries to enter will not depolarize the cell, but will only keep the cell from hyperpolarizing.

Stages of an Action Potential



Plotting voltage measured across the cell membrane against time, the events of the action potential can be related to specific changes in the membrane voltage. (1) At rest, the membrane voltage is -70 mV. (2) The membrane begins to depolarize when an external stimulus is applied. (3) The membrane voltage begins a rapid rise toward +30 mV. (4) The membrane voltage starts to return to a negative value. (5) Repolarization continues past the resting membrane voltage, resulting in hyperpolarization. (6) The membrane

voltage returns to the resting value shortly after hyperpolarization.

Propagation of the Action Potential

The action potential is initiated at the beginning of the axon, at what is called the axon hillock. There is a high density of voltage-gated Na⁺ channels so that rapid depolarization can take place here. The action potential then travels along the axon through propagation. In unmyelinated axons, the action potential is propagated because more voltage-gated Na+ channels are opened as the depolarization spreads. This spreading occurs because Na⁺ enters through the channel and moves along the inside of the cell membrane. As the Na⁺ moves, or flows, a short distance along the cell membrane, its positive charge depolarizes a little more of the cell membrane. As that depolarization spreads, new voltage-gated Na⁺ channels open and more ions rush into the cell, spreading the depolarization a little farther.

When myelination is present, the action potential propagates differently. Sodium ions that enter the cell at the initial segment start to spread along the length of the axon segment, but there are no voltage-gated Na⁺ channels until the first node of Ranvier. Because there is not constant opening of these channels along the axon segment, the depolarization spreads at an optimal speed. The distance between nodes is the optimal distance to keep the membrane still depolarized above threshold at the next node. As Na⁺ spreads along the inside of the membrane of the axon segment, the charge starts to dissipate. If the node were any farther down the axon, that depolarization would have fallen off too much for voltage-gated Na⁺ channels to be activated at the next node of Ranvier. If the nodes were any closer together, the speed of propagation would be slower.

Propagation along an unmyelinated axon is referred to as **continuous conduction**; along the length of a myelinated axon, it is **saltatory conduction**. Continuous conduction is slow because there are always voltage-gated Na⁺ channels opening, and more and more Na⁺ is rushing into the cell. Saltatory conduction is faster because the action potential

basically jumps from one node to the next (saltare = "to leap"), and the new influx of Na⁺ renews the depolarized membrane. Along with the myelination of the axon, the diameter of the axon can influence the speed of conduction. Much as water runs faster in a wide river than in a narrow creek, Na⁺-based depolarization spreads faster down a wide axon than down a narrow one. This concept is known as **resistance** and is generally true for electrical wires or plumbing, just as it is true for axons, although the specific conditions are different at the scales of electrons or ions versus water in a river.

Note:

Homeostatic Imbalances

Potassium Concentration

Glial cells, especially astrocytes, are responsible for maintaining the chemical environment of the CNS tissue. The concentrations of ions in the extracellular fluid are the basis for how the membrane potential is established and changes in electrochemical signaling. If the balance of ions is upset, drastic outcomes are possible.

Normally the concentration of K^+ is higher inside the neuron than outside. After the repolarizing phase of the action potential, K^+ leakage channels and the Na^+/K^+ pump ensure that the ions return to their original locations. Following a stroke or other ischemic event, extracellular K^+ levels are elevated. The astrocytes in the area are equipped to clear excess K^+ to aid the pump. But when the level is far out of balance, the effects can be irreversible.

Astrocytes can become reactive in cases such as these, which impairs their ability to maintain the local chemical environment. The glial cells enlarge and their processes swell. They lose their K⁺ buffering ability and the function of the pump is affected, or even reversed. If a Na⁺ gradient breaks down, this has a more important effect than interrupting the action potential. Glucose transport into cells is coupled with Na⁺ co-transport. When that is lost, the cell cannot get the energy it needs. In the central nervous system, carbohydrate metabolism is the only means of producing ATP. Elsewhere in the body, cells rely on carbohydrates, lipids, or amino acids to power mitochondrial ATP production. But the CNS does not store

lipids in adipocytes (fat cells) as an energy reserve. The lipids in the CNS are in the cell membranes of neurons and glial cells, notably as an integral component of myelin. Proteins in the CNS are crucial to neuronal function, in roles such as channels for electrical signaling or as part of the cytoskeleton. Those macromolecules are not used to power mitochondrial ATP production in neurons.

Note:



Visit this <u>site</u> to see a virtual neurophysiology lab, and to observe electrophysiological processes in the nervous system, where scientists directly measure the electrical signals produced by neurons. Often, the action potentials occur so rapidly that watching a screen to see them occur is not helpful. A speaker is powered by the signals recorded from a neuron and it "pops" each time the neuron fires an action potential. These action potentials are firing so fast that it sounds like static on the radio. Electrophysiologists can recognize the patterns within that static to understand what is happening. Why is the leech model used for measuring the electrical activity of neurons instead of using humans?

Chapter Review

The nervous system is characterized by electrical signals that are sent from one area to another. Whether those areas are close or very far apart, the signal must travel along an axon. The basis of the electrical signal is the controlled distribution of ions across the membrane. Transmembrane ion channels regulate when ions can move in or out of the cell, so that a precise

signal is generated. This signal is the action potential which has a very characteristic shape based on voltage changes across the membrane in a given time period.

The membrane is normally at rest with established Na⁺ and K⁺ concentrations on either side. A stimulus will start the depolarization of the membrane, and voltage-gated channels will result in further depolarization followed by repolarization of the membrane. A slight overshoot of hyperpolarization marks the end of the action potential. While an action potential is in progress, another cannot be generated under the same conditions. While the voltage-gated Na⁺ channel is inactivated, absolutely no action potentials can be generated. Once that channel has returned to its resting state, a new action potential is possible, but it must be started by a relatively stronger stimulus to overcome the K⁺ leaving the cell.

The action potential travels down the axon as voltage-gated ion channels are opened by the spreading depolarization. In unmyelinated axons, this happens in a continuous fashion because there are voltage-gated channels throughout the membrane. In myelinated axons, propagation is described as saltatory because voltage-gated channels are only found at the nodes of Ranvier and the electrical events seem to "jump" from one node to the next. Saltatory conduction is faster than continuous conduction, meaning that myelinated axons propagate their signals faster. The diameter of the axon also makes a difference as ions diffusing within the cell have less resistance in a wider space.

Glossary

absolute refractory period

time during an action period when another action potential cannot be generated because the voltage-gated Na⁺ channel is inactivated

activation gate

part of the voltage-gated Na⁺ channel that opens when the membrane voltage reaches threshold

continuous conduction

slow propagation of an action potential along an unmyelinated axon owing to voltage-gated Na⁺ channels located along the entire length of the cell membrane

depolarization

change in a cell membrane potential from rest toward zero

excitable membrane

cell membrane that regulates the movement of ions so that an electrical signal can be generated

gated

property of a channel that determines how it opens under specific conditions, such as voltage change or physical deformation

inactivation gate

part of a voltage-gated Na⁺ channel that closes when the membrane potential reaches +30 mV

leak channel

ion channel that opens randomly and is not gated to a specific event, also known as a non-gated channel

ligand-gated channels

another name for an ionotropic receptor for which a neurotransmitter is the ligand

mechanically gated channel

ion channel that opens when a physical event directly affects the structure of the protein

membrane potential

distribution of charge across the cell membrane, based on the charges of ions

refractory period

time after the initiation of an action potential when another action potential cannot be generated

relative refractory period

time during the refractory period when a new action potential can only be initiated by a stronger stimulus than the current action potential because voltage-gated K^+ channels are not closed

repolarization

return of the membrane potential to its normally negative voltage at the end of the action potential

resistance

property of an axon that relates to the ability of particles to diffuse through the cytoplasm; this is inversely proportional to the fiber diameter

resting membrane potential

the difference in voltage measured across a cell membrane under steady-state conditions, typically -70 mV

saltatory conduction

quick propagation of the action potential along a myelinated axon owing to voltage-gated Na⁺ channels being present only at the nodes of Ranvier

voltage-gated channel

ion channel that opens because of a change in the charge distributed across the membrane where it is located

OU Human Physiology: Synaptic Transmission and Neural Integration By the end of this section, you will be able to:

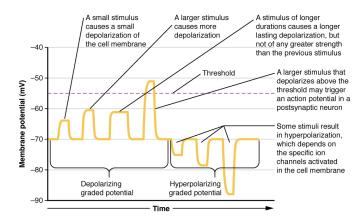
- Identify the location of graded potentials on the neuron
- Describe the purpose of a graded potential and its properties
- List the types of graded potentials
- Explain the purpose of an excitatory and inhibitory postsynaptic potentials
- Compare and contrast the mechanisms of excitatory and inhibitory postsynaptic potentials
- Compare and contrast spatial and temporal summation
- Distinguish between a chemical synapse and an electrical synapse
- Identify the components of a chemical synapse
- · Describe the events occurring at the synapse
- Recall from previous material the properties of an ionotropic and metabotropic receptor and relate this knowledge to ligand gated channels on the postsynaptic membrane
- Discuss the mechanism of acetylcholine synthesis and degradation
- · List the receptor types for acetylcholine
- Explain the mechanism for acetylcholine binding to nicotinic and metabotropic receptors
- List the receptor types for epinephrine and norepinephrine
- Discuss the affinities, second messenger system activation, and an example location for adrenergic receptors
- List the biogenic amines and discuss their importance
- Compare and contrast the receptor type, neurotransmitter elimination, and postsynaptic effect for each of the neurotransmitter systems

The electrical changes taking place within a neuron, as described in the previous section, are similar to a light switch being turned on. A stimulus starts the depolarization, but the action potential runs on its own once a threshold has been reached. The question is now, "What flips the light switch on?" Temporary changes to the cell membrane voltage can result from neurons receiving information from the environment, or from the action of one neuron on another. These special types of potentials influence a neuron and determine whether an action potential will occur or not. Many of these transient signals originate at the synapse.

Graded Potentials

Local changes in the membrane potential are called graded potentials and are associated with the dendrites and cell body of a neuron. Graded potentials will determine whether or not an action potential will occur. If the graded potentials are strong enough to reach the axon hillock this will trigger an action potential. To fully understand this concept, it is important to discuss the properties of graded potentials. First, graded potentials are decremental; they lose their strength as they move away from the site of stimulation and toward the axon hillock. Second, the magnitude of a graded potential is directly proportional to the strength of the stimulus. In other words, the amount of change in the membrane potential is determined by the size of the stimulus that causes it. In the example of testing the temperature of the shower, slightly warm water would only initiate a small change in a thermoreceptor, whereas hot water would cause a large amount of change in the membrane potential. Third, graded potentials can be excitatory or inhibitory. Graded potentials can be of two sorts, either they are depolarizing or hyperpolarizing ([link]). For a membrane at the resting potential, a graded potential represents a change in that voltage either above -70 mV or below -70 mV. Depolarizing graded potentials are often the result of Na⁺ or Ca²⁺ entering the cell. Both of these ions have higher concentrations outside the cell than inside; because they have a positive charge, they will move into the cell causing it to become less negative relative to the outside. Hyperpolarizing graded potentials can be caused by K⁺ leaving the cell or Cl⁻ entering the cell. If a positive charge moves out of a cell, the cell becomes more negative; if a negative charge enters the cell, the same thing happens.

Graded Potentials



Graded potentials are temporary changes in the membrane voltage, the characteristics of which depend on the size of the stimulus. Some types of stimuli cause depolarization of the membrane, whereas others cause hyperpolarization. It depends on the specific ion channels that are activated in the cell membrane.

Types of Graded Potentials

For the unipolar cells of sensory neurons—both those with free nerve endings and those within encapsulations—graded potentials develop in the dendrites that influence the generation of an action potential in the axon of the same cell. This is called a **generator potential**. For other sensory receptor cells, such as taste cells or photoreceptors of the retina, graded potentials in their membranes result in the release of neurotransmitters at synapses with sensory neurons. This is called a **receptor potential**. End plate potentials are also graded potentials that are generated on the end plate of skeletal muscle. Slow wave potentials and pacemaker potentials are also types of graded potentials. We will return to the various types of graded potentials at a later time. For now, we will focus on postsynaptic potentials.

A **postsynaptic potential (PSP)** is the graded potential in the dendrites and cell bodies of a neuron that synapse with other cells. Postsynaptic potentials can be depolarizing or hyperpolarizing. Depolarization in a postsynaptic potential is called an **excitatory postsynaptic potential (EPSP)** because it causes the membrane potential to move toward threshold. Hyperpolarization in a postsynaptic potential is an **inhibitory postsynaptic potential (IPSP)** because it causes the membrane potential to move away from threshold.

Summation

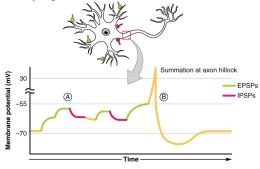
All types of graded potentials will result in small changes of either depolarization or hyperpolarization in the voltage of a membrane. These changes can lead to the neuron reaching threshold if the changes add together, or **summate**. The combined effects of different types of graded potentials are illustrated in [link]. If the total change in voltage in the membrane is a positive 15 mV, meaning that the membrane depolarizes from -70 mV to -55 mV, then the graded potentials will result in the membrane reaching threshold and an action potential will occur.

For receptor potentials, threshold is not a factor because the change in membrane potential for receptor cells directly causes neurotransmitter release. However, generator potentials can initiate action potentials in the sensory neuron axon, and postsynaptic potentials can initiate an action potential in the axon of other neurons. Graded potentials summate at a specific location at the beginning of the axon to initiate the action potential, namely the initial segment. For sensory neurons, which do not have a cell body between the dendrites and the axon, the initial

segment is directly adjacent to the dendritic endings. For all other neurons, the axon hillock is essentially the initial segment of the axon, and it is where summation takes place. These locations have a high density of voltage-gated Na⁺ channels that initiate the depolarizing phase of the action potential.

Summation can be spatial or temporal, meaning it can be the result of multiple graded potentials at different locations on the neuron, or all at the same place but separated in time. **Spatial summation** is related to associating the activity of different stimuli overlapping in time to a neuron when this occurs the graded potential from the first stimuli does not weaken before the next, thus the potentials can sum. **Temporal summation** occurs when the effects of the same stimuli is repeated close together in time, the potentials can sum. Spatial and temporal summation can act together, as well.

Postsynaptic Potential Summation



The result of summation of postsynaptic potentials is the overall change in the membrane potential. At point A, several different excitatory postsynaptic potentials add up to a large depolarization. At point B, a mix of excitatory and inhibitory postsynaptic potentials result in a different end result for the membrane potential.

Note:



Watch this <u>video</u> to learn about summation. The process of converting electrical signals to chemical signals and back requires subtle changes that can result in transient increases or decreases in membrane voltage. To cause a lasting change in the target cell, multiple signals are usually added together, or summated. Does spatial summation have to happen all at once, or can the separate signals arrive on the postsynaptic neuron at slightly different times? Explain your answer.

Synapses

There are two types of connections between electrically active cells, chemical synapses and electrical synapses. In a **chemical synapse**, a chemical signal—namely, a neurotransmitter—is released from one cell and it affects the

other cell. In an **electrical synapse**, there is a direct connection between the two cells so that ions can pass directly from one cell to the next. If one cell is depolarized in an electrical synapse, the joined cell also depolarizes because the ions pass between the cells. Chemical synapses involve the transmission of chemical information from one cell to the next. This section will concentrate on the chemical synapse.

Chemical synapses can occur between two neurons, a presynaptic and postsynaptic neuron or a neuron and an effector (skeletal muscle or a gland). When chemical synapses occur between two neurons they are named based on the structures of the neurons that are involved in the synapse. For example, an axodendritic synapse is a synapse that occurs between the axon of presynaptic neuron with the dendrite of the postsynaptic neuron or axosomatic where the synapse occurs between the axon of the presynaptic neuron with the cell body of the postsynaptic neuron or axoaxonic where the axons of both the presynaptic and postsynaptic neurons synapse. If the synapse occurs between a neuron and an effector we call this a neuroeffector junction. More specifically, a neuromuscular junction (NMJ) if the synapse is between a motor neuron and skeletal muscle. All synapses have common characteristics, which can be summarized in this list:

- presynaptic element
- neurotransmitter (packaged in vesicles—called sypatic vesicles)
- synaptic cleft
- · receptor proteins
- postsynaptic element
- · neurotransmitter elimination or re-uptake

For the NMJ, these characteristics are as follows: the presynaptic element is the motor neuron's axon terminals, the neurotransmitter is acetylcholine, the synaptic cleft is the space between the cells where the neurotransmitter diffuses, the receptor protein is the nicotinic acetylcholine receptor, the postsynaptic element is the sarcolemma of the muscle cell, and the neurotransmitter is eliminated by acetylcholinesterase. Other synapses are similar to this, and the specifics are different, but they all contain the same characteristics.

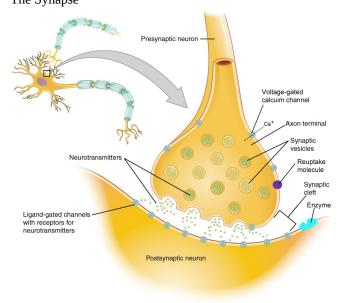
Neurotransmitter Release

[link] shows a synapse between a presynaptic and postsynaptic neuron. Before discussing the events at the synapse, it is important to understand the anatomy of the synapse.

- a. Neurotransmitters: The neurotransmitters are housed in the synaptic vesicles within the axon terminal of the presynaptic neuron after their synthesis via enzyme catalyzed reactions in the cytosol of the axon terminal. Eventually, these neurotransmitters will be released from the axon terminal via exocytosis
- b. Voltage-gated Calcium Channels: These voltage gated channels are located on the membrane of the presynaptic axon terminal. Please recall that these are voltage gated and therefore open in response to a change in the membrane potential. These channels will open when the axon terminal is depolarized.
- c. Calcium: There is a higher concentration of calcium in the ECF than ICF. Calcium is responsible for triggering the release of the neurotransmitters.
- d. Ligand-gated Channels: Ligand-gated channels are located on the membrane of the cell bodies and dendrites of postsynaptic cells. Please recall that these are ligand gated and respond when a ligand, in this case the neurotransmitter, binds to the channel. It is the result of this binding that will generate a postsynaptic potential on the postsynaptic cell.
- e. Enzyme: Enzymes are needed for degradation of the neurotransmitter once it has been released into the synaptic cleft. These enzymes can be found on the postsynaptic membrane.
- f. Reuptake molecule: When it is time for the neurotransmitter to be removed from the synaptic cleft it may use a reuptake molecule on the membrane of the axon terminal to be returned to the cytosol for recycling. This reuptake is an active transport mechanism. Alternatively, the reuptake molecule may uptake a product of neurotransmitter degradation that then could be used to synthesis more neurotransmitter once returned to the cytoplasm of the axon terminal.
- g. Synaptic Cleft: the space between the presynaptic neuron and postsynaptic cell.

Now that you have the anatomy of the synapse, let's focus in on the events occurring at the synapse. When an action potential reaches the axon terminals, voltage-gated Ca^{2+} channels in the membrane of the axon terminal open. Calcium influx occurs causing the concentration of calcium to increase inside the axon terminal, and the Ca^{2+} ions associate with proteins in the outer surface of neurotransmitter vesicles. The Ca^{2+} facilitates the merging of the vesicle with the presynaptic membrane so that the neurotransmitter is released through exocytosis into the small gap between the cells, the **synaptic cleft**.

Once in the synaptic cleft, the neurotransmitter diffuses the short distance to the postsynaptic membrane and binds to ligand-gated channels on the postsynaptic membrane. This ligand-gated channel is also a receptor that illustrates specificity such that specific neurotransmitters bind to specific ligand-gated channels like a lock and a key. Recall that receptor-ligand binding is reversible. Once the stimulus is removed from the presynaptic neuron, the neurotransmitter in the synaptic cleft must be removed. This process is dependent on the specific neurotransmitter but may include enzymatic degradation, reuptake, and/or diffusion away from the synaptic cleft ([link]). The Synapse



The synapse is a connection between a neuron and its postsynaptic cell. Ca²⁺ enters the presynaptic axon terminal to cause vesicle fusion and neurotransmitter release. The neurotransmitter diffuses across the synaptic cleft to bind to its receptor. The neurotransmitter is cleared from the synapse either by enzymatic degradation, neuronal reuptake, or diffusion away from the cleft.

Note:



Watch this <u>video</u> to learn about the release of a neurotransmitter. The action potential reaches the end of the axon, called the axon terminal, and a chemical signal is released to tell the target cell to do something—either to initiate a new action potential, or to suppress that activity. In a very short space, the electrical signal of the action potential is changed into the chemical signal of a neurotransmitter and then back to electrical changes in the target cell membrane. What is the importance of voltage-gated calcium channels in the release of neurotransmitters?

Neurotransmitters

The effect of neurotransmitters, and signaling chemicals in general, is entirely dependent on the receptor. Neurotransmitters bind to one of two classes of receptors at the cell surface, ionotropic or metabotropic ([link]). Ionotropic receptors are ligand-gated ion channels; meaning the receptor and the channel are the same protein. As a result, these channels are often referred to as 'fast' due to their quick opening due to the ligand binding. When the ligand binds, the channel will open allowing for ion movement which will alter the electrical properties of the cell. Examples of ionotropic receptors include the nicotinic receptor for acetylcholine or the glycine receptor. Metabotropic receptors on the other hand involve two separate proteins. In other words, the receptor and the ligand gated channel are two different proteins and are slower than an ionotropic receptor and are therefore often called 'slow' receptors. Here when the ligand binds to the receptor, this will activate a G-protein, recall that the G stands for guanosine and the G-protein is a complex of three subunits, alpha, beta, and gamma and is activated when the GDP is replaced by a GTP. From this point one of two things may happen, direct coupling or activation of a second messenger. Recall that direct coupling will result in the opening or closing of a protein channel which alters the electrical charge of the cell; whereas, activation of a second messenger systems.

There are several systems of neurotransmitters that are found at various synapses in the nervous system. These groups refer to the chemicals that are the neurotransmitters, and within the groups are specific systems.

The first group, which is a neurotransmitter system of its own, is the **cholinergic system**. It is the system based on acetylcholine (ACh); an important neurotransmitter involved in both the central and peripheral nervous systems, including the neuromuscular junction. Acetylcholine is synthesized in the axon terminal of presynaptic cells from two substrates, acetyl CoA and choline via choline acetyl transferase (CAT). Recall that Acetyl CoA is a two-carbon molecule produced as a result of pyruvate oxidation in cellular respiration. Choline however, cannot be synthesized and must be obtained from our diet. Acetylcholine is broken down when it binds to the enzyme acetylcholinesterase (AChE) which is located on either the presynaptic or postsynaptic membranes. When acetylcholine is degraded the products are acetate and choline. Choline uses the reuptake molecule on the presynaptic neuron to be reused in the synthesis of more acetylcholine; acetate diffuses away from the synapse and enters the blood.

The cholinergic system has two types of receptors, the **nicotinic receptor**, a type of ionotropic receptor, is found in the NMJ as well as other synapses. There is also an acetylcholine receptor known as the **muscarinic receptor**, a type of cholinergic. Both of these receptors are named for drugs that interact with the receptor in addition to acetylcholine. Nicotine will bind to the nicotinic receptor and activate it similar to acetylcholine. Muscarine, a product of certain mushrooms, will bind to the muscarinic receptor. However, nicotine will not bind to the muscarinic receptor and muscarine will not bind to the nicotinic receptor.

Another group of neurotransmitters are amino acids. This includes glutamate (Glu), GABA (gamma-aminobutyric acid, a derivative of glutamate), and glycine (Gly). These amino acids have an amino group and a carboxyl group in their chemical structures. Glutamate is one of the 20 amino acids that are used to make proteins. Each amino acid neurotransmitter would be part of its own system, namely the glutamatergic, GABAergic, and glycinergic systems. They each have their own receptors and do not interact with each other. Amino acid neurotransmitters are eliminated from the synapse by reuptake. A pump in the cell membrane of the presynaptic element, or sometimes a neighboring glial cell, will clear the amino acid from the synaptic cleft so that it can be recycled, repackaged in vesicles, and released again.

Another class of neurotransmitter is the **biogenic amine**, a group of neurotransmitters that are enzymatically made from amino acids. They have amino groups in them, but no longer have carboxyl groups and are therefore no

longer classified as amino acids. Biogenic amines play an important role in behavior and mental illness (i.e., bipolar disorder Schizophrenia, and depression.)

Serotonin is a biogenic amine made from tryptophan. It is the basis of the serotonergic system in the central nervous system, which has its own specific receptors. Serotonin is important in regulating sleep and our emotions. Serotonin is transported back into the presynaptic cell for repackaging.

Other biogenic amines are made from tyrosine, and include the catecholamines: dopamine, norepinephrine, and epinephrine. Dopamine is part of its own system, the dopaminergic system, which has dopamine receptors. Dopamine is removed from the synapse by transport proteins in the presynaptic cell membrane. Norepinephrine and epinephrine belong to the adrenergic neurotransmitter system. The two molecules are very similar and bind to the same receptors, which are referred to as alpha and beta adrenergic receptors. Norepinephrine and epinephrine are also transported back into the presynaptic cell. The chemical epinephrine (epi-= "on"; "-nephrine" = kidney) is also known as adrenaline (renal = "kidney"), and norepinephrine is sometimes referred to as noradrenaline. Recall that the adrenal gland produces epinephrine and norepinephrine to be released into the blood stream as hormones.

There are five different adrenergic receptors. Both epinephrine and norepinephrine bind to these receptors; however, their affinities may vary as well as the location of these receptors and the second messenger system activated as a result of the neurotransmitter binding ([link]).

Receptor	Affinity	Function	Tissues	
Alpha-one	NE>E	Activates IP ₃	Vascular smooth muscles, pupils	
Alpha-two	NE>E	Blocks cAMP production CNS, platelets, vascular smooth muscle,		
Beta-one	NE=E	Activates cAMP	CNS, cardiac, kidney	
Beta-two	E>NE	Activates cAMP	Some blood vessels, respiratory tract, uterus	
Beta-three	NE=E	Activates cAMP	Adipose	

The Adernergic Receptors

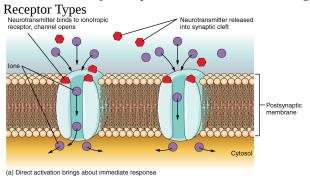
Histamine is also a neurotransmitter in the hypothalamus. Histamine is derived from the amino acid, histidine. Recall that histamine can also act as a paracrine ligand.

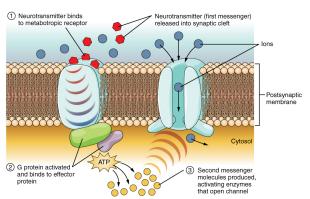
A **neuropeptide** is a neurotransmitter molecule made up of chains of amino acids connected by peptide bonds. This is what a protein is, but the term protein implies a certain length to the molecule. Some neuropeptides are quite short, such as met-enkephalin, which is five amino acids long. Others are long, such as beta-endorphin, which is 31 amino acids long. Neuropeptides are often released at synapses in combination with another neurotransmitters, and they often act as hormones in other systems of the body, such as antidiuretic hormone, oxytocin, and thyrotropin releasing hormone.

The effect of a neurotransmitter on the postsynaptic element is entirely dependent on the receptor protein. First, if there is no receptor protein in the membrane of the postsynaptic element, then the neurotransmitter has no effect. The depolarizing or hyperpolarizing effect is also dependent on the receptor. When acetylcholine binds to the nicotinic receptor, the postsynaptic cell is depolarized. This is because the receptor is a cation channel in which the sodium influx and potassium efflux occurs. However, there is more sodium entering the cell than K^+ leaving and the net effect is depolarization. However, when acetylcholine binds to the muscarinic receptor, of which there are several variants, it might cause depolarization or hyperpolarization of the target cell, depending on the specific target.

The amino acid neurotransmitters, glutamate, glycine, and GABA, are almost exclusively associated with just one effect. Glutamate is considered an excitatory amino acid, but only because Glu receptors in the adult cause depolarization of the postsynaptic cell. Glycine and GABA are considered inhibitory amino acids, again because their receptors cause hyperpolarization.

The biogenic amines have mixed effects. For example, the dopamine receptors that are classified as D1 receptors are excitatory whereas D2-type receptors are inhibitory. Biogenic amine receptors and neuropeptide receptors can have even more complex effects because some may not directly affect the membrane potential, but rather have an effect on gene transcription or other metabolic processes in the neuron. The characteristics of the various neurotransmitter systems presented in this section are organized in [link].





(b) Indirect activation involves a prolonged response, amplified over time

(a) An ionotropic receptor is a channel that opens when the neurotransmitter binds to it. (b) A metabotropic receptor is a complex that causes metabolic changes in the cell when the neurotransmitter binds to it (1). After binding, the G protein hydrolyzes GTP and moves to the effector protein (2). When the G protein contacts the effector protein, a second messenger is generated, such as cAMP (3). The second messenger can then go on to cause changes in the neuron, such as opening or closing ion channels, metabolic changes, and changes in gene transcription.

Characteristics of Neurotransmitter Systems						
System	Cholinergic	Amino acids	Biogenic amines	Neuropeptides		
Neurotransmitters	Acetylcholine	Glutamate, glycine, GABA	Serotonin (5-HT), dopamine, norepinephrine, (epinephrine), histamine	Met-enkephalin, beta-endorphin, VIP, Substance I etc.		
Receptors	Nicotinic and muscarinic receptors	Glu receptors, gly receptors, GABA receptors	5-HT receptors, D1 and D2 receptors, α- adrenergic and β- adrenergic receptors	Receptors are too numerous to list, but are specific to the peptides.		
Elimination	Degradation by acetylcholinesterase	Reuptake by neurons or glia	Reuptake by neurons	Degradation by enzymes called peptidases		
Postsynaptic effect	Nicotinic receptor causes depolarization. Muscarinic receptors can cause both depolarization or hyperpolarization depending on the subtype.	Glu receptors cause depolarization. Gly and GABA receptors cause hyperpolarization.	Depolarization or hyperpolarization depends on the specific receptor. For example, D1 receptors cause depolarization and D2 receptors cause hyperpolarization.	Depolarization o hyperpolarization depends on the specific receptor		

Note:

Disorders of the...

Nervous System

The underlying cause of some neurodegenerative diseases, such as Alzheimer's and Parkinson's, appears to be related to proteins—specifically, to proteins behaving badly. One of the strongest theories of what causes Alzheimer's disease is based on the accumulation of beta-amyloid plaques, dense conglomerations of a protein that is not functioning correctly. Parkinson's disease is linked to an increase in a protein known as alpha-synuclein that is toxic to the cells of the substantia nigra nucleus in the midbrain.

For proteins to function correctly, they are dependent on their three-dimensional shape. The linear sequence of amino acids folds into a three-dimensional shape that is based on the interactions between and among those amino acids. When the folding is disturbed, and proteins take on a different shape, they stop functioning correctly. But the disease is not necessarily the result of functional loss of these proteins; rather, these altered proteins start to accumulate and may become toxic. For example, in Alzheimer's, the hallmark of the disease is the accumulation of these amyloid plaques in the cerebral cortex. The term coined to describe this sort of disease is "proteopathy" and it includes other diseases. Creutzfeld-Jacob disease, the human variant of the prion disease known as mad cow disease in the bovine, also involves the accumulation of amyloid plaques, similar to Alzheimer's. Diseases of other organ systems can fall into this group as well, such as cystic fibrosis or type 2 diabetes. Recognizing the relationship between these diseases has suggested new therapeutic possibilities. Interfering with the accumulation of the proteins, and possibly as early as their original production within the cell, may unlock new ways to alleviate these devastating diseases.

Chapter Review

The basis of the electrical signal within a neuron is the action potential that propagates down the axon. For a neuron to generate an action potential, it needs to receive input from another source, either another neuron or a sensory stimulus. That input will result in opening ion channels in the neuron, resulting in a graded potential based on the strength of the stimulus. Graded potentials can be depolarizing or hyperpolarizing and can summate to affect the probability of the neuron reaching threshold.

Graded potentials can be the result of sensory stimuli. If the sensory stimulus is received by the dendrites of a unipolar sensory neuron, such as the sensory neuron ending in the skin, the graded potential is called a generator potential because it can directly generate the action potential in the initial segment of the axon. If the sensory stimulus is received by a specialized sensory receptor cell, the graded potential is called a receptor potential. Graded potentials produced by interactions between neurons at synapses are called postsynaptic potentials (PSPs). A depolarizing graded potential at a synapse is called an excitatory PSP, and a hyperpolarizing graded potential at a synapse is called an inhibitory PSP.

Synapses are the contacts between neurons, which can either be chemical or electrical in nature. Chemical synapses are far more common. At a chemical synapse, neurotransmitter is released from the presynaptic element and diffuses across the synaptic cleft. The neurotransmitter binds to a receptor protein and causes a change in the postsynaptic membrane (the PSP). The neurotransmitter must be inactivated or removed from the synaptic cleft so that the stimulus is limited in time.

The particular characteristics of a synapse vary based on the neurotransmitter system produced by that neuron. The cholinergic system is found at the neuromuscular junction and in certain places within the nervous system. Amino acids, such as glutamate, glycine, and gamma-aminobutyric acid (GABA) are used as neurotransmitters. Other neurotransmitters are the result of amino acids being enzymatically changed, as in the biogenic amines, or being covalently bonded together, as in the neuropeptides.

Interactive Link Questions

Exercise:

Problem:

Watch this <u>video</u> to learn about summation. The process of converting electrical signals to chemical signals and back requires subtle changes that can result in transient increases or decreases in membrane voltage. To cause a lasting change in the target cell, multiple signals are usually added together, or summated. Does spatial summation have to happen all at once, or can the separate signals arrive on the postsynaptic neuron at slightly different times? Explain your answer.

Solution:

A second signal from a separate presynaptic neuron can arrive slightly later, as long as it arrives before the first one dies off, or dissipates.

Exercise:

Problem:

Watch this <u>video</u> to learn about the release of a neurotransmitter. The action potential reaches the end of the axon, called the axon terminal, and a chemical signal is released to tell the target cell to do something, either initiate a new action potential, or to suppress that activity. In a very short space, the electrical signal of the action potential is changed into the chemical signal of a neurotransmitter, and then back to electrical changes in the target cell membrane. What is the importance of voltage-gated calcium channels in the release of neurotransmitters?

Solution:

The action potential depolarizes the cell membrane of the axon terminal, which contains the voltage-gated Ca^{2+} channel. That voltage change opens the channel so that Ca^{2+} can enter the axon terminal. Calcium ions make it possible for synaptic vesicles to release their contents through exocytosis.

Review Questions

Exercise:

Problem:

How much of a change in the membrane potential is necessary for the summation of postsynaptic potentials to result in an action potential being generated?

- a. +30 mV
- b. +15 mV
- c. +10 mV
- d. -15 mV

Solution:

В

Exercise:

Problem:

A channel opens on a postsynaptic membrane that causes a negative ion to enter the cell. What type of graded potential is this?

- a. depolarizing
- b. repolarizing
- c. hyperpolarizing
- d. non-polarizing

Solution:

C

Exercise:

Problem: What neurotransmitter is released at the neuromuscular junction?

- a. norepinephrine
- b. serotonin
- c. dopamine
- d. acetylcholine

Solution:

D

Exercise:

Problem: What type of receptor requires an effector protein to initiate a signal?

a. biogenic amine

- b. ionotropic receptor
- c. cholinergic system
- d. metabotropic receptor

Solution:

D

Exercise:

Problem: Which of the following neurotransmitters is associated with inhibition exclusively?

- a. GABA
- b. acetylcholine
- c. glutamate
- d. norepinephrine

Solution:

Α

Critical Thinking Questions

Exercise:

Problem:

If a postsynaptic cell has synapses from five different cells, and three cause EPSPs and two of them cause IPSPs, give an example of a series of depolarizations and hyperpolarizations that would result in the neuron reaching threshold.

Solution:

```
EPSP1 = +5 \text{ mV}, EPSP2 = +7 \text{ mV}, EPSP3 = +10 \text{ mV}, IPSP1 = -4 \text{ mV}, IPSP2 = -3 \text{ mV}. 5 + 7 + 10 - 4 - 3 = +15 \text{ mV}.
```

Exercise:

Problem:

Why is the receptor the important element determining the effect a neurotransmitter has on a target cell?

Solution:

Different neurotransmitters have different receptors. Thus, the type of receptor in the postsynaptic cell is what determines which ion channels open. Acetylcholine binding to the nicotinic receptor causes cations to cross the membrane. GABA binding to its receptor causes the anion chloride to cross the membrane.

Glossary

biogenic amine

class of neurotransmitters that are enzymatically derived from amino acids but no longer contain a carboxyl group

chemical synapse

connection between two neurons, or between a neuron and its target, where a neurotransmitter diffuses across a very short distance

cholinergic system

neurotransmitter system of acetylcholine, which includes its receptors and the enzyme acetylcholinesterase

effector protein

enzyme that catalyzes the generation of a new molecule, which acts as the intracellular mediator of the signal that binds to the receptor

electrical synapse

connection between two neurons, or any two electrically active cells, where ions flow directly through channels spanning their adjacent cell membranes

excitatory postsynaptic potential (EPSP)

graded potential in the postsynaptic membrane that is the result of depolarization and makes an action potential more likely to occur

generator potential

graded potential from dendrites of a unipolar cell which generates the action potential in the initial segment of that cell's axon

G protein

guanosine triphosphate (GTP) hydrolase that physically moves from the receptor protein to the effector protein to activate the latter

inhibitory postsynaptic potential (IPSP)

graded potential in the postsynaptic membrane that is the result of hyperpolarization and makes an action potential less likely to occur

metabotropic receptor

neurotransmitter receptor that involves a complex of proteins that cause metabolic changes in a cell

muscarinic receptor

type of acetylcholine receptor protein that is characterized by also binding to muscarine and is a metabotropic receptor

neuropeptide

neurotransmitter type that includes protein molecules and shorter chains of amino acids

nicotinic receptor

type of acetylcholine receptor protein that is characterized by also binding to nicotine and is an ionotropic receptor

postsynaptic potential (PSP)

graded potential in the postsynaptic membrane caused by the binding of neurotransmitter to protein receptors

receptor potential

graded potential in a specialized sensory cell that directly causes the release of neurotransmitter without an intervening action potential

spatial summation

combination of graded potentials across the neuronal cell membrane caused by signals from separate presynaptic elements that add up to initiate an action potential

summate

to add together, as in the cumulative change in postsynaptic potentials toward reaching threshold in the membrane, either across a span of the membrane or over a certain amount of time

synaptic cleft

small gap between cells in a chemical synapse where neurotransmitter diffuses from the presynaptic element to the postsynaptic element

temporal summation

combination of graded potentials at the same location on a neuron resulting in a strong signal from one input

OU Human Physiology: The Nervous System Introduction class="introduction" Human Nervous System

The ability to balance like an acrobat combines functions throughou t the nervous system. The central and peripheral divisions coordinate control of the body using the senses of balance, body position, and touch on the soles of the feet. (credit: Rhett Sutphin)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Relate the developmental processes of the embryonic nervous system to the adult structures.
- Name the regions and functions of the adult brain including functional areas
- Describe the regions of the spinal cord in cross-section
- Explain the relationship between the PNS and CNS
- List the function for cranial nerves I, II, VII, IX, and X
- State the number of spinal nerves and explain the naming system for spinal nerves

The nervous system is responsible for controlling much of the body, both through somatic (voluntary) and autonomic (involuntary) functions. The structures of the nervous system must be described in detail to understand how many of these functions are possible. There is a physiological concept known as localization of function that states that certain structures are specifically responsible for prescribed functions. It is an underlying concept in all of anatomy and physiology, but the nervous system illustrates the concept very well.

Fresh, unstained nervous tissue can be described as gray or white matter, and within those two types of tissue it can be very hard to see any detail. However, as specific regions and structures have been described, they were related to specific functions. Understanding these structures and the functions they perform requires a detailed description of the anatomy of the nervous system, delving deep into what the central and peripheral structures are.

The place to start this study of the nervous system is the beginning of the individual human life, within the womb. The embryonic development of the nervous system allows for a simple framework on which progressively more complicated structures can be built. With this framework in place, a thorough investigation of the nervous system is possible.

OU Human Physiology: The Embryologic Perspective By the end of this section, you will be able to:

• Explain the expansion of the ventricular system of the adult brain from the central canal of the neural tube

The brain is a complex organ composed of gray parts and white matter, which can be hard to distinguish. Starting from an embryologic perspective allows you to understand more easily how the parts relate to each other. The embryonic nervous system begins as a very simple structure—essentially just a straight line, which then gets increasingly complex. Looking at the development of the nervous system with a couple of early snapshots makes it easier to understand the whole complex system.

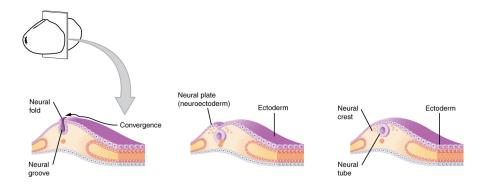
Many structures that appear to be adjacent in the adult brain are not connected, and the connections that exist may seem arbitrary. But there is an underlying order to the system that comes from how different parts develop. By following the developmental pattern, it is possible to learn what the major regions of the nervous system are.

The Neural Tube

To begin, a sperm cell and an egg cell fuse to become a fertilized egg. The fertilized egg cell, or zygote, starts dividing to generate the cells that make up an entire organism. Sixteen days after fertilization, the developing embryo's cells belong to one of three germ layers that give rise to the different tissues in the body. The endoderm, or inner tissue, is responsible for generating the lining tissues of various spaces within the body, such as the mucosae of the digestive and respiratory systems. The mesoderm, or middle tissue, gives rise to most of the muscle and connective tissues. Finally the ectoderm, or outer tissue, develops into the integumentary system (the skin) and the nervous system. It is probably not difficult to see that the outer tissue of the embryo becomes the outer covering of the body. But how is it responsible for the nervous system?

As the embryo develops, a portion of the ectoderm differentiates into a specialized region of neuroectoderm, which is the precursor for the tissue of the nervous system. Molecular signals induce cells in this region to differentiate into the neuroepithelium, forming a neural plate. The cells then begin to change shape, causing the tissue to buckle and fold inward ([link]). A neural groove forms, visible as a line along the dorsal surface of the embryo. The ridge-like edge on either side of the neural groove is referred as the neural fold. As the neural folds come together and converge, the underlying structure forms into a tube just beneath the ectoderm called the neural tube. Cells from the neural folds then separate from the ectoderm to form a cluster of cells referred to as the neural crest, which runs lateral to the neural tube. The neural crest migrates away from the nascent, or embryonic, central nervous system (CNS) that will form along the neural groove and develops into several parts of the peripheral nervous system (PNS), including the enteric nervous tissue. Many tissues that are not part of the nervous system also arise from the neural crest, such as craniofacial cartilage and bone, and melanocytes.

Early Embryonic Development of Nervous System



The neuroectoderm begins to fold inward to form the neural groove. As the two sides of the neural groove converge, they form the neural tube, which lies beneath the ectoderm. The anterior end of the neural tube will develop into the brain, and the posterior portion will become the spinal cord. The neural crest develops into peripheral structures.

At this point, the early nervous system is a simple, hollow tube. It runs from the anterior end of the embryo to the posterior end. Beginning at 25 days, the anterior end develops into the brain, and the posterior portion becomes the spinal cord. This is the most basic arrangement of tissue in the nervous system, and it gives rise to the more complex structures by the fourth week of development.

Primary Vesicles

As the anterior end of the neural tube starts to develop into the brain, it undergoes a couple of enlargements; the result is the production of sac-like vesicles. Similar to a child's balloon animal, the long, straight neural tube begins to take on a new shape. Three vesicles form at the first stage, which are called primary vesicles. These vesicles are given names that are based on Greek words, the main root word being *enkephalon*, which means "brain" (en- = "inside"; kephalon = "head"). The prefix to each generally corresponds to its position along the length of the developing nervous system.

The **prosencephalon** (pros- = "in front") is the forward-most vesicle, and the term can be loosely translated to mean **forebrain**. The **mesencephalon** (mes- = "middle") is the next vesicle, which can be called the **midbrain**. The third vesicle at this stage is the **rhombencephalon**. The first part of this word is also the root of the word rhombus, which is a geometrical figure with four sides of equal length (a square is a rhombus with 90° angles). Whereas prosencephalon and mesencephalon translate into the English words forebrain and midbrain, there is not a word for "four-sided-figure-brain." However, the third vesicle can be called the **hindbrain**. One way of thinking about how the brain is arranged is to use these three regions—forebrain, midbrain, and hindbrain—which are based on the primary vesicle stage of development ([link]a).

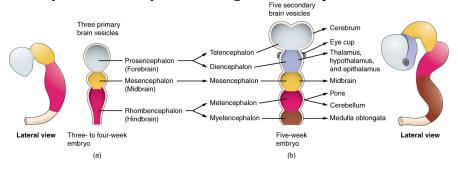
Secondary Vesicles

The brain continues to develop, and the vesicles differentiate further (see [link]b). The three primary vesicles become five secondary vesicles. The prosencephalon enlarges into two new vesicles called the **telencephalon** and the **diencephalon**. The telecephalon will become the cerebrum. The diencephalon gives rise to several adult structures; two that will be important are the thalamus and the hypothalamus. In the embryonic diencephalon, a structure known as the eye cup develops, which will eventually become the retina, the nervous tissue of the eye called the retina. This is a rare example of nervous tissue developing as part of the CNS structures in the embryo, but becoming a peripheral structure in the fully formed nervous system.

The mesencephalon does not differentiate into any finer divisions. The midbrain is an established region of the brain at the primary vesicle stage of development and remains that way. The rest of the brain develops around it and constitutes a large percentage of the mass of the brain. Dividing the brain into forebrain, midbrain, and hindbrain is useful in considering its developmental pattern, but the midbrain is a small proportion of the entire brain, relatively speaking.

The rhombencephalon develops into the **metencephalon** and **myelencephalon**. The metencephalon corresponds to the adult structure known as the pons and also gives rise to the cerebellum. The cerebellum (from the Latin meaning "little brain") accounts for about 10 percent of the mass of the brain and is an important structure in itself. The most significant connection between the cerebellum and the rest of the brain is at the pons, because the pons and cerebellum develop out of the same vesicle. The myelencephalon corresponds to the adult structure known as the medulla oblongata. The structures that come from the mesencephalon and rhombencephalon, except for the cerebellum, are collectively considered the **brain stem**, which specifically includes the midbrain, pons, and medulla.

Primary and Secondary Vesicle Stages of Development



The embryonic brain develops complexity through enlargements of the neural tube called vesicles; (a) The primary vesicle stage has three regions, and (b) the secondary vesicle stage has five regions.

Note:



Watch this <u>animation</u> to examine the development of the brain, starting with the neural tube. As the anterior end of the neural tube develops, it enlarges into the primary vesicles that establish the forebrain, midbrain, and hindbrain. Those structures continue to develop throughout the rest of embryonic development and into adolescence. They are the basis of the structure of the fully developed adult brain. How would you describe the difference in the relative sizes of the three regions of the brain when comparing the early (25th embryonic day) brain and the adult brain?

Spinal Cord Development

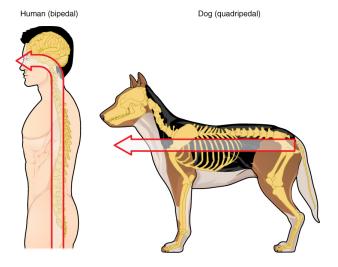
While the brain is developing from the anterior neural tube, the spinal cord is developing from the posterior neural tube. However, its structure does not differ from the basic layout of the neural tube. It is a long, straight cord with a small, hollow space down the center. The neural tube is defined in terms of its anterior versus posterior portions, but it also has a dorsal—ventral dimension. As the neural tube separates from the rest of the ectoderm, the side closest to the surface is dorsal, and the deeper side is ventral.

As the spinal cord develops, the cells making up the wall of the neural tube proliferate and differentiate into the neurons and glia of the spinal cord. The dorsal tissues will be associated with sensory functions, and the ventral tissues will be associated with motor functions.

Relating Embryonic Development to the Adult Brain

Embryonic development can help in understanding the structure of the adult brain because it establishes a framework on which more complex structures can be built. First, the neural tube establishes the anterior—posterior dimension of the nervous system, which is called the **neuraxis**. The embryonic nervous system in mammals can be said to have a standard arrangement. Humans (and other primates, to some degree) make this complicated by standing up and walking on two legs. The anterior—posterior dimension of the neuraxis overlays the superior—inferior dimension of the body. However, there is a major curve between the brain stem and forebrain, which is called the **cephalic flexure**. Because of this, the neuraxis starts in an inferior position—the end of the spinal cord—and ends in an anterior position, the front of the cerebrum. If this is confusing, just imagine a four-legged animal standing up on two legs. Without the flexure in the brain stem, and at the top of the neck, that animal would be looking straight up instead of straight in front ([link]).

Human Neuraxis



The mammalian nervous system is arranged with the neural tube running along an anterior to posterior axis, from nose to tail for a four-legged animal like a dog. Humans, as two-legged animals, have a bend in the neuraxis between the brain stem and the diencephalon, along with a bend in the neck, so that the eyes and the face are oriented forward.

In summary, the primary vesicles help to establish the basic regions of the nervous system: forebrain, midbrain, and hindbrain. These divisions are useful in certain situations, but they are not equivalent regions. The midbrain is small compared with the hindbrain and particularly the forebrain. The secondary vesicles go on to establish the major regions of the adult nervous system that will be followed in this text. The telencephalon is the cerebrum, which is the major portion of the human brain. The diencephalon continues to be referred to by this Greek name, because there is no better term for it (dia- = "through"). The diencephalon is between the cerebrum and the rest of the nervous system and can be described as the region through which all projections have to pass between the cerebrum and everything else. The brain stem includes the midbrain, pons, and medulla, which correspond to the mesencephalon, metencephalon, and myelencephalon. The cerebellum, being a large portion of the brain, is considered a separate region. [link] connects the different stages of development to the adult structures of the CNS.

One other benefit of considering embryonic development is that certain connections are more obvious because of how these adult structures are related. The retina, which began as part of the diencephalon, is primarily connected to the diencephalon. The eyes are just inferior to the anterior-most part of the cerebrum, but the optic nerve extends back to the thalamus as the optic tract, with branches into a region of the hypothalamus. There is also a connection of the optic tract to the midbrain, but the mesencephalon is adjacent to the diencephalon, so that is not difficult to imagine. The cerebellum originates out of the metencephalon, and its largest white

matter connection is to the pons, also from the metencephalon. There are connections between the cerebellum and both the medulla and midbrain, which are adjacent structures in the secondary vesicle stage of development. In the adult brain, the cerebellum seems close to the cerebrum, but there is no direct connection between them.

Another aspect of the adult CNS structures that relates to embryonic development is the ventricles—open spaces within the CNS where cerebrospinal fluid circulates. They are the remnant of the hollow center of the neural tube. The four ventricles and the tubular spaces associated with them can be linked back to the hollow center of the embryonic brain (see [link]).

Stages of Embryonic Development						
Neural tube	Primary vesicle stage	Secondary vesicle stage	Adult structures	Ventricles		
Anterior neural tube	Prosencephalon	Telencephalon	Cerebrum	Lateral ventricles		
Anterior neural tube	Prosencephalon	Diencephalon	Diencephalon	Third ventricle		
Anterior neural tube	Mesencephalon	Mesencephalon	Midbrain	Cerebral aqueduct		
Anterior neural tube	Rhombencephalon	Metencephalon	Pons cerebellum	Fourth ventricle		
Anterior neural tube	Rhombencephalon	Myelencephalon	Medulla	Fourth ventricle		
Posterior neural tube			Spinal cord	Central canal		

Note:

Disorders of the...

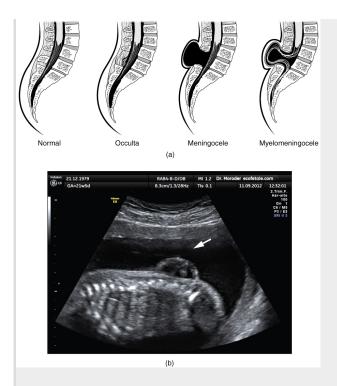
Nervous System

Early formation of the nervous system depends on the formation of the neural tube. A groove forms along the dorsal surface of the embryo, which becomes deeper until its edges meet and close off to form the tube. If this fails to happen, especially in the posterior region where the spinal cord forms, a developmental defect called spina bifida occurs. The closing of the neural tube is important for more than just the proper formation of the nervous system. The surrounding tissues are dependent on the correct development of the tube. The connective tissues surrounding the CNS can be involved as well.

There are three classes of this disorder: occulta, meningocele, and myelomeningocele ([link]). The first type, spina bifida occulta, is the mildest because the vertebral bones do not fully surround the spinal cord, but the spinal cord itself is not affected. No functional differences may be noticed, which is what the word occulta means; it is hidden spina bifida. The other two types both involve the formation of a cyst—a fluid-filled sac of the connective tissues that cover the spinal cord called the meninges. "Meningocele" means that the meninges protrude through the spinal column but nerves may not be involved and few symptoms are present, though complications may arise later in life. "Myelomeningocele" means that the meninges protrude and spinal nerves are involved, and therefore severe neurological symptoms can be present.

Often surgery to close the opening or to remove the cyst is necessary. The earlier that surgery can be performed, the better the chances of controlling or limiting further damage or infection at the opening. For many children with meningocele, surgery will alleviate the pain, although they may experience some functional loss. Because the myelomeningocele form of spina bifida involves more extensive damage to the nervous tissue, neurological damage may persist, but symptoms can often be handled. Complications of the spinal cord may present later in life, but overall life expectancy is not reduced.

Spinal Bifida



(a) Spina bifida is a birth defect of the spinal cord caused when the neural tube does not completely close, but the rest of development continues. The result is the emergence of meninges and neural tissue through the vertebral column. (b) Fetal myelomeningocele is evident in this ultrasound taken at 21 weeks.

Note:



Watch this <u>video</u> to learn about the white matter in the cerebrum that develops during childhood and adolescence. This is a composite of MRI images taken of the brains of people from 5 years of age through 20 years of age, demonstrating how the cerebrum changes. As the color changes to blue, the ratio of gray matter to white matter changes. The caption for the video describes it as "less gray matter," which is another way of saying "more white matter."

If the brain does not finish developing until approximately 20 years of age, can teenagers be held responsible for behaving badly?

Chapter Review

The development of the nervous system starts early in embryonic development. The outer layer of the embryo, the ectoderm, gives rise to the skin and the nervous system. A specialized region of this layer, the neuroectoderm, becomes a groove that folds in and becomes the neural tube beneath the dorsal surface of the embryo. The anterior end of the neural tube develops into the brain, and the posterior region becomes the spinal cord. Tissues at the edges of the neural groove, when it closes off, are called the neural crest and migrate through the embryo to give rise to PNS structures as well as some non-nervous tissues.

The brain develops from this early tube structure and gives rise to specific regions of the adult brain. As the neural tube grows and differentiates, it enlarges into three vesicles that correspond to the forebrain, midbrain, and hindbrain regions of the adult brain. Later in development, two of these three vesicles differentiate further, resulting in five vesicles. Those five vesicles can be aligned with the four major regions of the adult brain. The cerebrum is formed directly from the telencephalon. The diencephalon is the only region that keeps its embryonic name. The mesencephalon, metencephalon, and myelencephalon become the brain stem. The cerebellum also develops from the metencephalon and is a separate region of the adult brain.

The spinal cord develops out of the rest of the neural tube and retains the tube structure, with the nervous tissue thickening and the hollow center becoming a very small central canal through the cord. The rest of the hollow center of the neural tube corresponds to open spaces within the brain called the ventricles, where cerebrospinal fluid is found.

Glossary

brain stem

region of the adult brain that includes the midbrain, pons, and medulla oblongata and develops from the mesencephalon, metencephalon, and myelencephalon of the embryonic brain

cephalic flexure

curve in midbrain of the embryo that positions the forebrain ventrally

diencephalon

region of the adult brain that retains its name from embryonic development and includes the thalamus and hypothalamus

forebrain

anterior region of the adult brain that develops from the prosencephalon and includes the cerebrum and diencephalon

hindbrain

posterior region of the adult brain that develops from the rhombencephalon and includes the pons, medulla oblongata, and cerebellum

mesencephalon

primary vesicle of the embryonic brain that does not significantly change through the rest of embryonic development and becomes the midbrain

metencephalon

secondary vesicle of the embryonic brain that develops into the pons and the cerebellum

midbrain

middle region of the adult brain that develops from the mesencephalon

myelencephalon

secondary vesicle of the embryonic brain that develops into the medulla

neuraxis

central axis to the nervous system, from the posterior to anterior ends of the neural tube; the inferior tip of the spinal cord to the anterior surface of the cerebrum

prosencephalon

primary vesicle of the embryonic brain that develops into the forebrain, which includes the cerebrum and diencephalon

rhombencephalon

primary vesicle of the embryonic brain that develops into the hindbrain, which includes the pons, cerebellum, and medulla

telencephalon

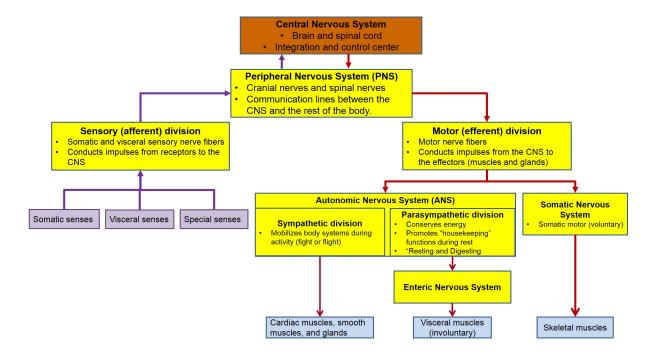
secondary vesicle of the embryonic brain that develops into the cerebrum

OU Human Physiology: The Central Nervous System By the end of this section, you will be able to:

- Name the four major regions of the adult brain
- Briefly explain the function of the basal nuclei, basal forebrain, and limbic cortex
- Name the four lobes of the cerebral cortex
- Describe the function and location for each of the functional areas
- Describe the connections between the cerebrum and brain stem through the diencephalon, and from those regions into the spinal cord
- Explain the arrangement of gray and white matter in the spinal cord and cerebrum/cerebral cortex
- Describe the function of dorsal, lateral, and ventral horn
- List the functions of the subcortical nuclei, hippocampus, and amygdala
- List the structures that makeup the diencephalon
- Explain the function of the thalamus
- List the functions of the hypothalamus
- List the structures that makeup the brain stem
- Briefly explain the purpose of the brain stem

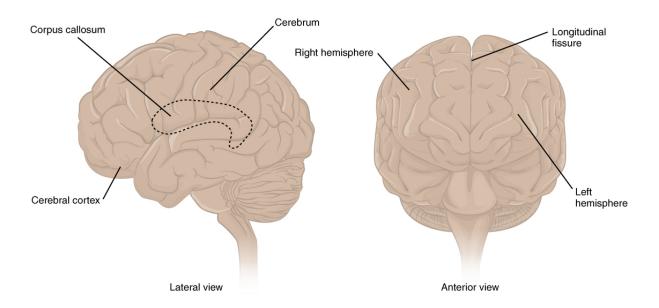
The brain and the spinal cord make-up the central nervous system (CNS), and they represent the main organs of the nervous system ([link]). The spinal cord is a single structure, whereas the adult brain is described in terms of four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. A person's conscious experiences are based on neural activity in the brain. The regulation of homeostasis is governed by a specialized region in the brain. The coordination of reflexes depends on the integration of sensory and motor pathways in the cerebrum. Terms that are used frequently in the central nervous system include nuclei which are clusters of cell bodies and pathways and tracts which are axons that travel in bundles.

Organization of the Nervous System



The Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the **cerebrum** ([link]). The wrinkled portion is the **cerebral cortex**, and the rest of the structure is beneath that outer covering. There is a large separation between the two sides of the cerebrum called the **longitudinal fissure**. It separates the cerebrum into two distinct halves, a right and left **cerebral hemisphere**. Deep within the cerebrum, the white matter of the **corpus callosum** provides the major pathway for communication between the two hemispheres of the cerebral cortex. The Cerebrum



The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.

Many of the higher neurological functions, such as memory, emotion, and consciousness, are the result of cerebral function. The complexity of the cerebrum is different across vertebrate species. The cerebrum of the most primitive vertebrates is not much more than the connection for the sense of smell. In mammals, the cerebrum comprises the outer gray matter that is the cortex (from the Latin word meaning "bark of a tree") and several deep nuclei that belong to three important functional groups. The **basal nuclei** are responsible for cognitive processing, the most important function being that associated with planning movements. The **basal forebrain** contains nuclei that are important in learning and memory. The **limbic cortex** is the region of the cerebral cortex that is part of the **limbic system**, a collection of structures involved in emotion, memory, and behavior.

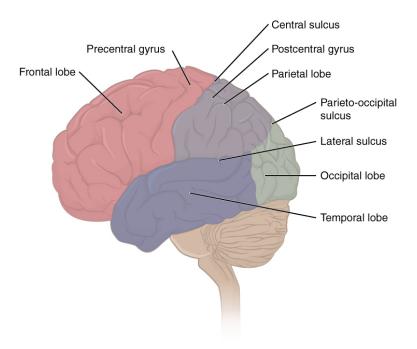
Cerebral Cortex

The cerebrum is covered by a continuous layer of gray matter that wraps around either side of the forebrain—the cerebral cortex. This thin, extensive region of wrinkled gray matter is responsible for the higher functions of the nervous system. A gyrus (plural = gyri) is the ridge of one of those wrinkles, and a sulcus (plural = sulci) is the groove between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex.

The head is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cortex were peeled off of the cerebrum and laid out flat, its surface area would be roughly equal to one square meter.

The folding of the cortex maximizes the amount of gray matter in the cranial cavity. During embryonic development, as the telencephalon expands within the skull, the brain goes through a regular course of growth that results in everyone's brain having a similar pattern of folds. The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes ([link]). The lateral sulcus that separates the **temporal lobe** from the other regions is one such landmark. Superior to the lateral sulcus are the **parietal lobe** and **frontal lobe**, which are separated from each other by the central sulcus. The posterior region of the cortex is the **occipital lobe**, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, an obvious landmark separating the parietal and occipital lobes is called the parieto-occipital sulcus. The fact that there is no obvious anatomical border between these lobes is consistent with the functions of these regions being interrelated.

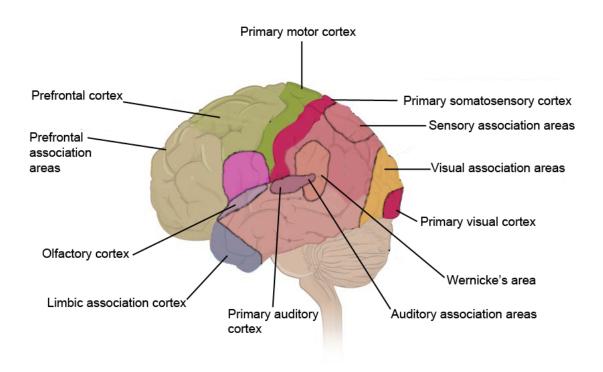
Lobes of the Cerebral Cortex



The cerebral cortex is divided into four lobes. Extensive folding increases the surface area available for cerebral functions.

Different regions of the cerebral cortex can be associated with particular functions, a concept known as localization of function. In the early 1900s, a German neuroscientist named Korbinian Brodmann performed an extensive study of the microscopic anatomy—the cytoarchitecture—of the cerebral cortex and divided the cortex into 52 separate regions on the basis of the histology of the cortex. His work resulted in a system of classification known as **Brodmann's areas**, which is still used today to describe the anatomical distinctions within the cortex. We will refer to these areas as functional areas ([link]).

Functional Areas of the Cerebral Cortex



Functional Areas of the Cerebral Cortex

Temporal lobe

Auditory and taste sensations are received by the temporal lobes. The primary auditory cortex perceives sound quality such as loudness and tone, whereas the surrounding auditory association area processes the sounds so they can be interpreted such as music, speech or other sounds. The olfactory cortex perceives taste quality. We will return to the primary auditory cortex and its association area as well as the olfactory cortex when we discuss hearing and taste.

The limbic association area is associated with the bottom of the temporal lobe.. This area is concerned primarily with motivation, emotion, and is extensively involved in memory.

Occipital lobe

The occipital lobe contains the primary visual cortex. This is where visual information is first processed. After this initial processing it is sent to the surrounding visual association areas for even more complex processing. We

will return to the primary visual cortex and its association area when we discuss vision.

Parietal lobe

The parietal lobe contains the somatosensory cortex and sensory association areas. The parietal lobe is primarily responsible for receiving and processing somesthetic sensation (somethetic means "body feelings") and proprioception. Somesthetic sensations come from the surface of the body, such as touch, pressure, heat, cold, and pain whereas proprioception is awareness of body position. Being aware of touch, pressure, and temperature, or pain is detected by the thalamus, but the somatosensory cortex goes beyond a simple awareness. The somatosensory cortex localizes the source and perceives the level of intensity. This information is then sent to the sensory association areas for even further analysis and integration of sensory information. Information regarding these sensations is sent to the somatosensory cortex on the parietal lobe for processing.

At the junction of the parietal, temporal, and occipital lobes is Wernicke's area. This area, just like Broca's is only on the left side of the brain. Wernicke's area is important is language comprehension whether it is spoken or written. It is also responsible for formulating coherent patterns of speech that are transferred to Broca's area via nerve fibers which then controls the act of speaking.

Frontal lobe

The frontal lobes are responsible for voluntary motor activity, speaking ability, and elaboration of thought. More specifically, the rear portion of the frontal lobe next to the somatosensory cortex is the primary motor cortex. This cortex controls voluntary movement produced by skeletal muscles. However, the movement is controlled by opposite sides of the brain due to the neuronal tracts crossing over before passing down the spinal cord to the efferent motor neuron that triggers skeletal muscle contraction. For example, the contraction of the right calf muscle is controlled by the left side of the frontal lobe. The area in front of this cortex is the premotor cortex; it is important in orienting the body and arms toward a specific target. In order to do so; however, it must be informed of the body's momentary position in relation to the target wo it can command the primary

motor cortex to produce appropriate skeletal muscle contraction for bringing about the desired movement. The prefrontal association area lies in the anterior most region of the frontal lobe. This is the area of the brain important for planning for voluntary activity, decision making, creativity, and personality traits. On the left side of the frontal lobe is Broca's area which governs speaking ability as it controls the muscles necessary for speaking.

Subcortical structures

Beneath the cerebral cortex are sets of nuclei known as **subcortical nuclei** that augment cortical processes. The nuclei of the basal forebrain serve as the primary location for acetylcholine production, which modulates the overall activity of the cortex, possibly leading to greater attention to sensory stimuli. Alzheimer's disease is associated with a loss of neurons in the basal forebrain. The **hippocampus** and **amygdala** are medial-lobe structures that, along with the adjacent cortex, are involved in long-term memory formation and emotional responses. The basal nuclei are a set of nuclei in the cerebrum responsible for comparing cortical processing with the general state of activity in the nervous system to influence the likelihood of movement taking place. For example, while a student is sitting in a classroom listening to a lecture, the basal nuclei will keep the urge to jump up and scream from actually happening. (The basal nuclei are also referred to as the basal ganglia, although that is potentially confusing because the term ganglia is typically used for peripheral structures.)

Note:

Everyday Connections

The Myth of Left Brain/Right Brain

There is a persistent myth that people are "right-brained" or "left-brained," which is an oversimplification of an important concept about the cerebral hemispheres. There is some lateralization of function, in which the left side of the brain is devoted to language function and the right side is devoted to spatial and nonverbal reasoning. Whereas these functions are

predominantly associated with those sides of the brain, there is no monopoly by either side on these functions. Many pervasive functions, such as language, are distributed globally around the cerebrum. Some of the support for this misconception has come from studies of split brains. A drastic way to deal with a rare and devastating neurological condition (intractable epilepsy) is to separate the two hemispheres of the brain. After sectioning the corpus callosum, a split-brained patient will have trouble producing verbal responses on the basis of sensory information processed on the right side of the cerebrum, leading to the idea that the left side is responsible for language function. However, there are well-documented cases of language functions lost from damage to the right side of the brain. The deficits seen in damage to the left side of the brain are classified as aphasia, a loss of speech function; damage on the right side can affect the use of language. Right-side damage can result in a loss of ability to understand figurative aspects of speech, such as jokes, irony, or metaphors. Nonverbal aspects of speech can be affected by damage to the right side, such as facial expression or body language, and right-side damage can lead to a "flat affect" in speech, or a loss of emotional expression in speech—sounding like a robot when talking.

The Diencephalon

The diencephalon is the one region of the adult brain that retains its name from embryologic development. The etymology of the word diencephalon translates to "through brain." It is the connection between the cerebrum and the rest of the nervous system, with one exception. The rest of the brain, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon. Output from the cerebrum passes through the diencephalon; the single exception is the system associated with **olfaction**, or the sense of smell, which connects directly with the cerebrum.

The diencephalon is deep beneath the cerebrum and constitutes the walls of the third ventricle. The diencephalon can be described as any region of the brain with "thalamus" in its name. The two major regions of the diencephalon are the thalamus itself and the hypothalamus ([link]). There are other structures, such as the epithalamus, which contains the pineal gland, or the subthalamus, which includes the subthalamic nucleus that is part of the basal nuclei.

Thalamus

The **thalamus** is a collection of nuclei that relay information between the cerebral cortex and the periphery, spinal cord, or brain stem. All sensory information, except for the sense of smell, passes through the thalamus before processing by the cortex. Axons from the peripheral sensory organs, or intermediate nuclei, synapse in the thalamus, and thalamic neurons project directly to the cerebrum. It is a requisite synapse in any sensory pathway, except for olfaction. The thalamus does not just pass the information on, it also processes that information. For example, the portion of the thalamus that receives visual information will influence what visual stimuli are important, or what receives attention.

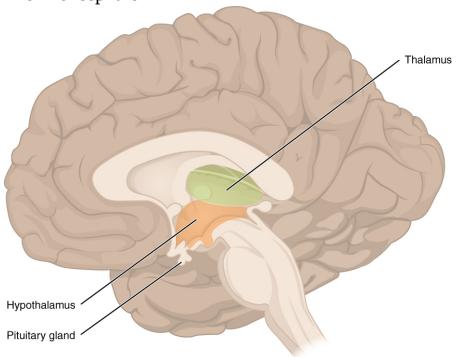
The cerebrum also sends information down to the thalamus, which usually communicates motor commands. This involves interactions with the cerebellum and other nuclei in the brain stem. The cerebrum interacts with the basal nuclei, which involves connections with the thalamus. The primary output of the basal nuclei is to the thalamus, which relays that output to the cerebral cortex. The cortex also sends information to the thalamus that will then influence the effects of the basal nuclei.

Hypothalamus

Inferior and slightly anterior to the thalamus is the **hypothalamus**, the other major region of the diencephalon. The hypothalamus is a collection of nuclei that are largely involved in regulating homeostasis. The hypothalamus is the executive region in charge of the autonomic nervous system and the endocrine system through its regulation of the anterior

pituitary gland. Other parts of the hypothalamus are involved in memory and emotion as part of the limbic system.

The Diencephalon



The diencephalon is composed primarily of the thalamus and hypothalamus, which together define the walls of the third ventricle. The thalami are two elongated, ovoid structures on either side of the midline that make contact in the middle. The hypothalamus is inferior and anterior to the thalamus, culminating in a sharp angle to which the pituitary gland is attached.

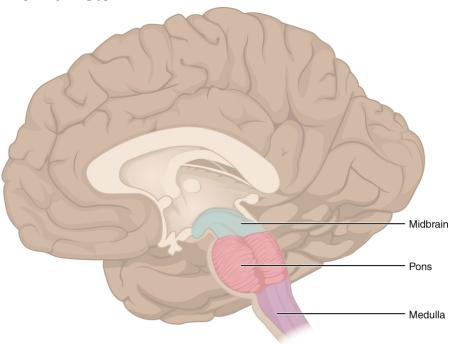
Brain Stem

The midbrain and hindbrain (composed of the pons and the medulla) are collectively referred to as the brain stem ([link]). The structure emerges from the ventral surface of the forebrain as a tapering cone that connects the brain to the spinal cord. Attached to the brain stem, but considered a

separate region of the adult brain, is the cerebellum. The midbrain coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces. The pons is the main connection with the cerebellum. The pons and the medulla regulate several crucial functions, including the cardiovascular and respiratory systems and rates.

The cranial nerves connect through the brain stem and provide the brain with the sensory input and motor output associated with the head and neck, including most of the special senses. The major ascending and descending pathways between the spinal cord and brain, specifically the cerebrum, pass through the brain stem.

The Brain Stem



The brain stem comprises three regions: the midbrain, the pons, and the medulla.

Midbrain

One of the original regions of the embryonic brain, the midbrain is a small region between the thalamus and pons. It is separated into the tectum and tegmentum, from the Latin words for roof and floor, respectively. The cerebral aqueduct passes through the center of the midbrain, such that these regions are the roof and floor of that canal.

The tectum is composed of four bumps known as the colliculi (singular = colliculus), which means "little hill" in Latin. The inferior colliculus is the inferior pair of these enlargements and is part of the auditory brain stem pathway. Neurons of the inferior colliculus project to the thalamus, which then sends auditory information to the cerebrum for the conscious perception of sound. The superior colliculus is the superior pair and combines sensory information about visual space, auditory space, and somatosensory space. Activity in the superior colliculus is related to orienting the eyes to a sound or touch stimulus. If you are walking along the sidewalk on campus and you hear chirping, the superior colliculus coordinates that information with your awareness of the visual location of the tree right above you. That is the correlation of auditory and visual maps. If you suddenly feel something wet fall on your head, your superior colliculus integrates that with the auditory and visual maps and you know that the chirping bird just relieved itself on you. You want to look up to see the culprit, but do not.

The tegmentum is continuous with the gray matter of the rest of the brain stem. Throughout the midbrain, pons, and medulla, the tegmentum contains the nuclei that receive and send information through the cranial nerves, as well as regions that regulate important functions such as those of the cardiovascular and respiratory systems.

Pons

The word pons comes from the Latin word for bridge. It is visible on the anterior surface of the brain stem as the thick bundle of white matter attached to the cerebellum. The pons is the main connection between the cerebellum and the brain stem. The bridge-like white matter is only the anterior surface of the pons; the gray matter beneath that is a continuation

of the tegmentum from the midbrain. Gray matter in the tegmentum region of the pons contains neurons receiving descending input from the forebrain that is sent to the cerebellum.

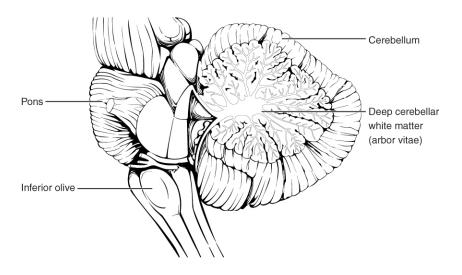
Medulla

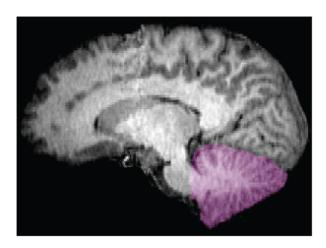
The medulla is the region known as the myelencephalon in the embryonic brain. The initial portion of the name, "myel," refers to the significant white matter found in this region—especially on its exterior, which is continuous with the white matter of the spinal cord. The tegmentum of the midbrain and pons continues into the medulla because this gray matter is responsible for processing cranial nerve information. A diffuse region of gray matter throughout the brain stem, known as the **reticular formation**, is related to sleep and wakefulness, such as general brain activity and attention.

The Cerebellum

The **cerebellum**, as the name suggests, is the "little brain." It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain ([link]). The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain.

The Cerebellum





The cerebellum is situated on the posterior surface of the brain stem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.

Descending fibers from the cerebrum have branches that connect to neurons in the pons. Those neurons project into the cerebellum, providing a copy of

motor commands sent to the spinal cord. Sensory information from the periphery, which enters through spinal or cranial nerves, is copied to a nucleus in the medulla known as the inferior olive. Fibers from this nucleus enter the cerebellum and are compared with the descending commands from the cerebrum. If the primary motor cortex of the frontal lobe sends a command down to the spinal cord to initiate walking, a copy of that instruction is sent to the cerebellum. Sensory feedback from the muscles and joints, proprioceptive information about the movements of walking, and sensations of balance are sent to the cerebellum through the inferior olive and the cerebellum compares them. If walking is not coordinated, perhaps because the ground is uneven or a strong wind is blowing, then the cerebellum sends out a corrective command to compensate for the difference between the original cortical command and the sensory feedback. The output of the cerebellum is into the midbrain, which then sends a descending input to the spinal cord to correct the messages going to skeletal muscles.

The Spinal Cord

The description of the CNS is concentrated on the structures of the brain, but the spinal cord is another major organ of the system. Whereas the brain develops out of expansions of the neural tube into primary and then secondary vesicles, the spinal cord maintains the tube structure and is only specialized into certain regions. As the spinal cord continues to develop in the newborn, anatomical features mark its surface. The anterior midline is marked by the anterior median fissure, and the posterior midline is marked by the posterior median sulcus. Axons enter the posterior side through the dorsal (posterior) nerve root, which marks the posterolateral sulcus on either side. The axons emerging from the anterior side do so through the ventral (anterior) nerve root. Note that it is common to see the terms dorsal (dorsal = "back") and ventral (ventral = "belly") used interchangeably with posterior and anterior, particularly in reference to nerves and the structures of the spinal cord. You should learn to be comfortable with both.

On the whole, the posterior regions are responsible for sensory functions and the anterior regions are associated with motor functions. This comes from the initial development of the spinal cord, which is divided into the basal plate and the alar plate. The basal plate is closest to the ventral midline of the neural tube, which will become the anterior face of the spinal cord and gives rise to motor neurons. The alar plate is on the dorsal side of the neural tube and gives rise to neurons that will receive sensory input from the periphery.

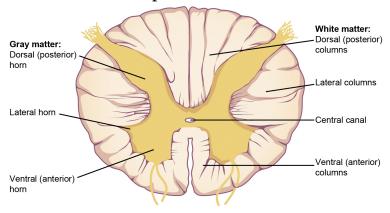
The length of the spinal cord is divided into regions that correspond to the regions of the vertebral column. The name of a spinal cord region corresponds to the level at which spinal nerves pass through the intervertebral foramina. Immediately adjacent to the brain stem is the cervical region, followed by the thoracic, then the lumbar, and finally the sacral region. The spinal cord is not the full length of the vertebral column because the spinal cord does not grow significantly longer after the first or second year, but the skeleton continues to grow. The nerves that emerge from the spinal cord pass through the intervertebral formina at the respective levels. As the vertebral column grows, these nerves grow with it and result in a long bundle of nerves that resembles a horse's tail and is named the **cauda equina**. The sacral spinal cord is at the level of the upper lumbar vertebral bones. The spinal nerves extend from their various levels to the proper level of the vertebral column.

Gray Horns

In cross-section, the gray matter of the spinal cord has the appearance of an ink-blot test, with the spread of the gray matter on one side replicated on the other—a shape reminiscent of a bulbous capital "H." As shown in [link], the gray matter is subdivided into regions that are referred to as horns. The **dorsal horn** is responsible for sensory processing. The **ventral horn** sends out motor signals to the skeletal muscles. The **lateral horn**, which is only found in the thoracic, upper lumbar, and sacral regions, is the central component of the sympathetic division of the autonomic nervous system.

Some of the largest neurons of the spinal cord are the multipolar motor neurons in the anterior horn. The fibers that cause contraction of skeletal muscles are the axons of these neurons. The motor neuron that causes contraction of the big toe, for example, is located in the sacral spinal cord. The axon that has to reach all the way to the belly of that muscle may be a meter in length. The neuronal cell body that maintains that long fiber must be quite large, possibly several hundred micrometers in diameter, making it one of the largest cells in the body.

Cross-section of Spinal Cord





The cross-section of a thoracic spinal cord segment shows the posterior, anterior, and lateral horns of gray matter, as well as the posterior, anterior, and lateral columns of white matter. LM × 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

White Columns

Just as the gray matter is separated into horns, the white matter of the spinal cord is separated into columns. Ascending tracts of nervous system fibers in these columns carry sensory information up to the brain, whereas descending tracts carry motor commands from the brain. Looking at the spinal cord longitudinally, the columns extend along its length as continuous bands of white matter. Between the two posterior horns of gray matter are the posterior columns. Between the two anterior horns, and bounded by the axons of motor neurons emerging from that gray matter area, are the anterior columns. The white matter on either side of the spinal cord, between the posterior horn and the axons of the anterior horn neurons, are the lateral columns. The posterior columns are composed of axons of ascending tracts. The anterior and lateral columns are composed of many different groups of axons of both ascending and descending tracts—the latter carrying motor commands down from the brain to the spinal cord to control output to the periphery.

Note:



Watch this <u>video</u> to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

Note:

Disorders of the...

Basal Nuclei

Parkinson's disease is a disorder of the basal nuclei, specifically of the substantia nigra, that demonstrates the effects of the direct and indirect pathways. Parkinson's disease is the result of neurons in the substantia nigra pars compacta dying. These neurons release dopamine into the striatum. Without that modulatory influence, the basal nuclei are stuck in the indirect pathway, without the direct pathway being activated. The direct pathway is responsible for increasing cortical movement commands. The increased activity of the indirect pathway results in the hypokinetic disorder of Parkinson's disease.

Parkinson's disease is neurodegenerative, meaning that neurons die that cannot be replaced, so there is no cure for the disorder. Treatments for Parkinson's disease are aimed at increasing dopamine levels in the striatum. Currently, the most common way of doing that is by providing the amino acid L-DOPA, which is a precursor to the neurotransmitter dopamine and can cross the blood-brain barrier. With levels of the precursor elevated, the remaining cells of the substantia nigra pars compacta can make more neurotransmitter and have a greater effect. Unfortunately, the patient will become less responsive to L-DOPA treatment as time progresses, and it can cause increased dopamine levels elsewhere in the brain, which are associated with psychosis or schizophrenia.

Note:



Visit this <u>site</u> for a thorough explanation of Parkinson's disease.

Note:



Compared with the nearest evolutionary relative, the chimpanzee, the human has a brain that is huge. At a point in the past, a common ancestor gave rise to the two species of humans and chimpanzees. That evolutionary history is long and is still an area of intense study. But something happened to increase the size of the human brain relative to the chimpanzee. Read this <u>article</u> in which the author explores the current understanding of why this happened.

According to one hypothesis about the expansion of brain size, what tissue might have been sacrificed so energy was available to grow our larger brain? Based on what you know about that tissue and nervous tissue, why would there be a trade-off between them in terms of energy use?

Note:

Disorders of the Central Nervous System

The supply of blood to the brain is crucial to its ability to perform many functions. Without a steady supply of oxygen, and to a lesser extent glucose, the nervous tissue in the brain cannot keep up its extensive electrical activity. These nutrients get into the brain through the blood, and if blood flow is interrupted, neurological function is compromised. The common name for a disruption of blood supply to the brain is a stroke. It is caused by a blockage to an artery in the brain. The blockage is from some type of embolus: a blood clot, a fat embolus, or an air bubble. When the blood cannot travel through the artery, the surrounding tissue that is deprived starves and dies. Strokes will often result in the loss of very specific functions. A stroke in the lateral medulla, for example, can cause a loss in the ability to swallow. Sometimes, seemingly unrelated functions will be lost because they are dependent on structures in the same region.

Along with the swallowing in the previous example, a stroke in that region could affect sensory functions from the face or extremities because important white matter pathways also pass through the lateral medulla. Loss of blood flow to specific regions of the cortex can lead to the loss of specific higher functions, from the ability to recognize faces to the ability to move a particular region of the body. Severe or limited memory loss can be the result of a temporal lobe stroke.

Related to strokes are transient ischemic attacks (TIAs), which can also be called "mini-strokes." These are events in which a physical blockage may be temporary, cutting off the blood supply and oxygen to a region, but not to the extent that it causes cell death in that region. While the neurons in that area are recovering from the event, neurological function may be lost. Function can return if the area is able to recover from the event. Recovery from a stroke (or TIA) is strongly dependent on the speed of treatment. Often, the person who is present and notices something is wrong must then make a decision. The mnemonic **FAST** helps people remember what to look for when someone is dealing with sudden losses of neurological function. If someone complains of feeling "funny," check these things quickly: Look at the person's face. Does he or she have problems moving \mathbf{F} ace muscles and making regular facial expressions? Ask the person to raise his or her **A**rms above the head. Can the person lift one arm but not the other? Has the person's **S**peech changed? Is he or she slurring words or having trouble saying things? If any of these things have happened, then it is $\underline{\mathbf{T}}$ ime to call for help.

Sometimes, treatment with blood-thinning drugs can alleviate the problem, and recovery is possible. If the tissue is damaged, the amazing thing about the nervous system is that it is adaptable. With physical, occupational, and speech therapy, victims of strokes can recover, or more accurately relearn, functions.

Chapter Review

The adult brain is separated into four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. The cerebrum is the

largest portion and contains the cerebral cortex and subcortical nuclei. It is divided into two halves by the longitudinal fissure.

The cortex is separated into the frontal, parietal, temporal, and occipital lobes. The frontal lobe is responsible for motor functions, from planning movements through executing commands to be sent to the spinal cord and periphery. The most anterior portion of the frontal lobe is the prefrontal cortex, which is associated with aspects of personality through its influence on motor responses in decision-making.

The other lobes are responsible for sensory functions. The parietal lobe is where somatosensation is processed. The occipital lobe is where visual processing begins, although the other parts of the brain can contribute to visual function. The temporal lobe contains the cortical area for auditory processing, but also has regions crucial for memory formation.

Nuclei beneath the cerebral cortex, known as the subcortical nuclei, are responsible for augmenting cortical functions. The basal nuclei receive input from cortical areas and compare it with the general state of the individual through the activity of a dopamine-releasing nucleus. The output influences the activity of part of the thalamus that can then increase or decrease cortical activity that often results in changes to motor commands. The basal forebrain is responsible for modulating cortical activity in attention and memory. The limbic system includes deep cerebral nuclei that are responsible for emotion and memory.

The diencephalon includes the thalamus and the hypothalamus, along with some other structures. The thalamus is a relay between the cerebrum and the rest of the nervous system. The hypothalamus coordinates homeostatic functions through the autonomic and endocrine systems.

The cerebellum is connected to the brain stem, primarily at the pons, where it receives a copy of the descending input from the cerebrum to the spinal cord. It can compare this with sensory feedback input through the medulla and send output through the midbrain that can correct motor commands for coordination.

Glossary

amygdala

nucleus deep in the temporal lobe of the cerebrum that is related to memory and emotional behavior

ascending tract

central nervous system fibers carrying sensory information from the spinal cord or periphery to the brain

basal forebrain

nuclei of the cerebrum related to modulation of sensory stimuli and attention through broad projections to the cerebral cortex, loss of which is related to Alzheimer's disease

basal nuclei

nuclei of the cerebrum (with a few components in the upper brain stem and diencephalon) that are responsible for assessing cortical movement commands and comparing them with the general state of the individual through broad modulatory activity of dopamine neurons; largely related to motor functions, as evidenced through the symptoms of Parkinson's and Huntington's diseases

Brodmann's areas

mapping of regions of the cerebral cortex based on microscopic anatomy that relates specific areas to functional differences, as described by Brodmann in the early 1900s

cauda equina

bundle of spinal nerve roots that descend from the lower spinal cord below the first lumbar vertebra and lie within the vertebral cavity; has the appearance of a horse's tail

cerebellum

region of the adult brain connected primarily to the pons that developed from the metencephalon (along with the pons) and is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord

cerebral cortex

outer gray matter covering the forebrain, marked by wrinkles and folds known as gyri and sulci

cerebral hemisphere

one half of the bilaterally symmetrical cerebrum

corpus callosum

large white matter structure that connects the right and left cerebral hemispheres

cerebrum

region of the adult brain that develops from the telencephalon and is responsible for higher neurological functions such as memory, emotion, and consciousness

corpus callosum

large white matter structure that connects the right and left cerebral hemispheres

descending tract

central nervous system fibers carrying motor commands from the brain to the spinal cord or periphery

dorsal horn

gray matter region of the spinal cord in which sensory input arrives, sometimes referred to as the posterior horn

frontal lobe

region of the cerebral cortex directly beneath the frontal bone of the

hippocampus

gray matter deep in the temporal lobe that is very important for longterm memory formation

hypothalamus

major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis

lateral horn

region of the spinal cord gray matter in the thoracic, upper lumbar, and sacral regions that is the central component of the sympathetic division of the autonomic nervous system

limbic cortex

collection of structures of the cerebral cortex that are involved in emotion, memory, and behavior and are part of the larger limbic system

limbic system

structures at the edge (limit) of the boundary between the forebrain and hindbrain that are most associated with emotional behavior and memory formation

longitudinal fissure

large separation along the midline between the two cerebral hemispheres

occipital lobe

region of the cerebral cortex directly beneath the occipital bone of the

olfaction

special sense responsible for smell, which has a unique, direct connection to the cerebrum

parietal lobe

region of the cerebral cortex directly beneath the parietal bone of the

reticular formation

diffuse region of gray matter throughout the brain stem that regulates sleep, wakefulness, and states of consciousness

subcortical nucleus

all the nuclei beneath the cerebral cortex, including the basal nuclei and the basal forebrain

temporal lobe

region of the cerebral cortex directly beneath the temporal bone of the cranium

thalamus

major region of the diencephalon that is responsible for relaying information between the cerebrum and the hindbrain, spinal cord, and periphery

ventral (anterior) nerve root

axons emerging from the anterior or lateral horns of the spinal cord

OU Human Physiology: The Peripheral Nervous System By the end of this section, you will be able to:

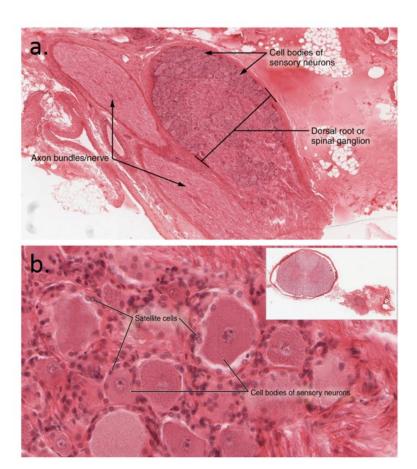
- Explain the relationship between the PNS and CNS
- List the function for cranial nerves I, II, VII, IX, and X
- State the number of spinal nerves
- Explain the naming system for spinal nerves
- Define ganglia
- Define nerve

The central nervous system does not act alone; it must communicate with the peripheral nervous system (PNS). The CNS receives signals from the PNS and sends signals back to the PNS so we can respond to a stimulus. Thus, the PNS is the communication line between the CNS and the rest of the body.

The peripheral nervous system (PNS) is not as contained as the central nervous system (CNS) because it is defined as everything that is not the central nervous system. Some peripheral structures are incorporated into the other organs of the body. In describing the anatomy of the PNS, it is necessary to describe the common structures, the nerves and the ganglia, as they are found in various parts of the body. Many of the neural structures that are incorporated into other organs are features of the digestive system; these structures are known as the **enteric nervous system** and are a special subset of the PNS.

Ganglia

A ganglion is a group of neuron cell bodies in the periphery. Ganglia can be categorized, for the most part, as either sensory ganglia or autonomic ganglia, referring to their primary functions. The most common type of sensory ganglion is a **dorsal (posterior) root ganglion**. These ganglia are the cell bodies of neurons with axons that are sensory endings in the periphery, such as in the skin, and that extend into the CNS through the dorsal nerve root. The ganglion is an enlargement of the nerve root. Under microscopic inspection, it can be seen to include the cell bodies of the neurons, as well as bundles of fibers that are the posterior nerve root ([link]). The cells of the dorsal root ganglion are unipolar cells, classifying them by shape. Also, the small round nuclei of satellite cells can be seen surrounding—as if they were orbiting—the neuron cell bodies. Spinal Cord and Ganglia

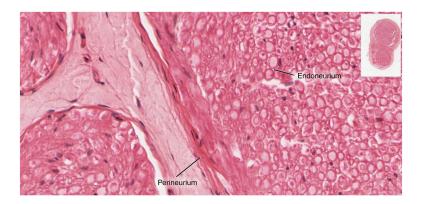


a.)The cell bodies of sensory neurons, which are unipolar neurons by shape, are seen in this photomicrograph. Also, the fibrous region is composed of the axons of these neurons that are passing through the ganglion to be part of the dorsal nerve root (tissue source: canine). LM × 40. b.).) The slide includes both a cross-section of the lumbar spinal cord and a section of the dorsal root ganglion (tissue source: canine). LM × 1600. LM × 40. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

Nerves

Bundles of axons in the PNS are referred to as nerves. These structures in the periphery are different than the central counterpart, called a tract. Nerves are composed of more than just nervous tissue. They have connective tissues invested in their structure, as well as blood vessels supplying the tissues with nourishment. Nerves are associated with the region of the CNS to which they are connected, either as cranial nerves connected to the brain or spinal nerves connected to the spinal cord.

Close-Up of Nerve Trunk



Zoom in on this slide of a nerve trunk to examine the endoneurium, perineurium, and epineurium in greater detail (tissue source: simian). LM \times 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the University of Michigan WebScope at http://virtualslides.med.umich.edu/Histology/Basic%20Tissues/Nervous%20Tissue/068_HISTO_40X.svs/view.ap_ml to explore the tissue sample in greater detail. With what structures in a skeletal muscle are the endoneurium, perineurium, and epineurium comparable?

Cranial Nerves

The nerves attached to the brain are the cranial nerves, which are primarily responsible for the sensory and motor functions of the head and neck (one of these nerves targets organs in the thoracic and abdominal cavities as part of the parasympathetic nervous system). There are twelve cranial nerves, which are designated CNI through CNXII for "Cranial Nerve," using Roman numerals for 1 through 12. They can be classified as sensory nerves, motor nerves, or a combination of both, meaning that the axons in these nerves originate out of sensory ganglia external to the cranium or motor nuclei within the brain stem. Sensory axons enter the brain to synapse in a nucleus. Motor axons connect to skeletal muscles of the head or neck. Three of the nerves are solely composed of sensory fibers; five are strictly motor; and the remaining four are mixed nerves.

Learning the cranial nerves is a tradition in anatomy courses, and students have always used mnemonic devices to remember the nerve names. A traditional mnemonic is the rhyming couplet, "On Old Olympus' Towering Tops/A Finn And German Viewed Some Hops," in which the initial letter of each word corresponds to the initial letter in the name of each nerve. The names of the nerves have changed over the years to reflect current usage and more accurate naming. An exercise to help learn this sort of information is to generate a mnemonic using words that have personal significance. The names of the cranial nerves are listed in [link] along with a brief description of their function, their source (sensory ganglion or motor nucleus), and their target (sensory nucleus or skeletal muscle). They are listed here with a brief explanation of each nerve ([link]).

The **offactory nerve** and **optic nerve** are responsible for the sense of smell and vision, respectively. The **oculomotor nerve** is responsible for eye movements by controlling four of the **extraocular muscles**. It is also responsible for lifting the upper eyelid when the eyes point up, and for pupillary constriction. The **trochlear nerve** and the **abducens nerve** are both responsible for eye movement, but do so by controlling different extraocular muscles. The **trigeminal nerve** is responsible for cutaneous sensations of the face and controlling the muscles of mastication. The **facial nerve** is responsible for the muscles involved in facial expressions, as well as part of the sense of taste and the production of saliva. The **vestibulocochlear nerve** is responsible for the senses of hearing and balance. The **glossopharyngeal nerve** is responsible for controlling muscles in the oral cavity and upper throat, as well as part of the sense of taste and the production of saliva. The **vagus nerve** is responsible for contributing to homeostatic control of the organs of the thoracic and upper abdominal cavities. The **spinal accessory nerve** is responsible for controlling the muscles of the neck, along with cervical spinal nerves. The **hypoglossal nerve** is responsible for controlling the muscles of the lower throat and tongue.

The Cranial Nerves

Olfactory nerve I

Oculomotor nerve III

Trochlear nerve IV

Abducens nerve VI

Vestibulocochlear nerve VIII

Hypoglossal nerve XII

Accessory nerve XI

The anatomical arrangement of the roots of the cranial nerves observed from an inferior view of the brain.

Three of the cranial nerves also contain autonomic fibers, and a fourth is almost purely a component of the autonomic system. The oculomotor, facial, and glossopharyngeal nerves contain fibers that contact autonomic ganglia. The oculomotor fibers initiate pupillary constriction, whereas the facial and glossopharyngeal fibers both initiate salivation. The vagus nerve primarily targets autonomic ganglia in the thoracic and upper abdominal cavities.

Note:



Visit this <u>site</u> to read about a man who wakes with a headache and a loss of vision. His regular doctor sent him to an ophthalmologist to address the vision loss. The ophthalmologist recognizes a greater problem and immediately sends him to the emergency room. Once there, the patient undergoes a large battery of tests, but a definite cause cannot be found. A specialist recognizes the problem as meningitis, but the question is what caused it originally. How can that be cured? The loss of vision comes from swelling around the optic nerve, which probably presented as a bulge on the inside of the eye. Why is swelling related to meningitis going to push on the optic nerve?

Another important aspect of the cranial nerves that lends itself to a mnemonic is the functional role each nerve plays. The nerves fall into one of three basic groups. They are sensory, motor, or both (see [link]). The sentence, "Some Say Marry Money But My Brother Says Brains Beauty Matter More," corresponds to the basic function of each nerve. The first, second, and eighth nerves are purely sensory: the olfactory (CNI), optic (CNII), and vestibulocochlear (CNVIII) nerves. The three eye-movement nerves are all motor: the oculomotor (CNIII), trochlear (CNIV), and abducens (CNVI). The spinal accessory (CNXI) and hypoglossal (CNXII) nerves are also strictly motor. The remainder of the nerves contain both sensory and motor fibers. They are the trigeminal (CNV), facial (CNVII), glossopharyngeal (CNIX), and vagus (CNX) nerves. The nerves that convey both are often related to each other. The trigeminal and facial nerves both concern the face; one concerns the sensations and the other concerns the muscle movements. The facial and glossopharyngeal nerves are both responsible for conveying gustatory, or taste, sensations as well as controlling salivary glands. The vagus nerve is involved in visceral responses to taste, namely the gag reflex. This is not an exhaustive list of what these combination nerves do, but there is a thread of relation between them.

Cranial Nerves					
Mnemonic	#	Name	Function (S/M/B)	Central connection (nuclei)	
On	I	Olfactory	Smell (S)	Olfactory bulb	
Old	II	Optic	Vision (S)	Hypothalamus/thalamus/midbrain	
Olympus'	III	Oculomotor	Eye movements (M)	Oculomotor nucleus	
Towering	IV	Trochlear	Eye movements (M)	Trochlear nucleus	
Tops	V	Trigeminal	Sensory/motor – face (B)	Trigeminal nuclei in the midbrain, pons, and medulla	
A	VI	Abducens	Eye movements (M)	Abducens nucleus	
Finn	VII	Facial	Motor – face, Taste (B)	Facial nucleus, solitary nucleus, superior salivatory nucleus	

Cranial Nerves						
Mnemonic	#	Name	Function (S/M/B)	Central connection (nuclei)		
And	VIII	Auditory (Vestibulocochlear)	Hearing/balance (S)	Cochlear nucleus, Vestibular nucleus/cerebellum		
German	IX	Glossopharyngeal	Motor – throat Taste (B)	Solitary nucleus, inferior salivatory nucleus, nucleus ambiguus		
Viewed	X	Vagus	Motor/sensory – viscera (autonomic) (B)	Medulla		
Some	XI	Spinal Accessory	Motor – head and neck (M)	Spinal accessory nucleus		
Hops	XII	Hypoglossal	Motor – lower throat (M)	Hypoglossal nucleus		

Spinal Nerves

The nerves connected to the spinal cord are the spinal nerves. The arrangement of these nerves is much more regular than that of the cranial nerves. All of the spinal nerves are combined sensory and motor axons that separate into two nerve roots. The sensory axons enter the spinal cord as the dorsal nerve root. The motor fibers, both somatic and autonomic, emerge as the ventral nerve root. The dorsal root ganglion for each nerve is an enlargement of the spinal nerve.

There are 31 spinal nerves, named for the level of the spinal cord at which each one emerges. There are eight pairs of cervical nerves designated C1 to C8, twelve thoracic nerves designated T1 to T12, five pairs of lumbar nerves designated L1 to L5, five pairs of sacral nerves designated S1 to S5, and one pair of coccygeal nerves. The nerves are numbered from the superior to inferior positions, and each emerges from the vertebral column through the intervertebral foramen at its level. The first nerve, C1, emerges between the first cervical vertebra and the occipital bone. The second nerve, C2, emerges between the first and second cervical vertebrae. The same occurs for C3 to C7, but C8 emerges between the seventh cervical vertebra and the first thoracic vertebra. For the thoracic and lumbar nerves, each one emerges between the vertebra that has the same designation and the next vertebra in the column. The sacral nerves emerge from the sacral foramina along the length of that unique vertebra.

Note:

Aging and the...

Nervous System

Anosmia is the loss of the sense of smell. It is often the result of the olfactory nerve being severed, usually because of blunt force trauma to the head. The sensory neurons of the olfactory epithelium have a limited lifespan of approximately one to four months, and new ones are made on a regular basis. The new neurons extend their axons into the CNS by growing along the existing fibers of the olfactory nerve. The ability of these neurons to be replaced is lost with age. Age-related anosmia is not the result of impact trauma to the head, but rather a slow loss of the sensory neurons with no new neurons born to replace them.

Smell is an important sense, especially for the enjoyment of food. There are only five tastes sensed by the tongue, and two of them are generally thought of as unpleasant tastes (sour and bitter). The rich sensory experience of food is the result of odor molecules associated with the food, both as food is moved into the mouth, and therefore passes under the nose, and when it is chewed and molecules are released to move up the pharynx into the posterior nasal cavity. Anosmia results in a loss of the enjoyment of food.

As the replacement of olfactory neurons declines with age, anosmia can set in. Without the sense of smell, many sufferers complain of food tasting bland. Often, the only way to enjoy food is to add seasoning that can be sensed on the tongue, which usually means adding table salt. The problem with this solution, however, is that this increases sodium intake, which can lead to cardiovascular problems through water retention and the associated increase in blood pressure.

Chapter Review

The PNS is composed of the groups of neurons (ganglia) and bundles of axons (nerves) that are outside of the brain and spinal cord. Ganglia are of two types, sensory or autonomic. Sensory ganglia contain unipolar sensory neurons and are found on the dorsal root of all spinal nerves as well as associated with many of the cranial nerves. Autonomic ganglia are in the sympathetic chain, the associated paravertebral or prevertebral ganglia, or in terminal ganglia near or within the organs controlled by the autonomic nervous system.

Nerves are classified as cranial nerves or spinal nerves on the basis of their connection to the brain or spinal cord, respectively. The twelve cranial nerves can be strictly sensory in function, strictly motor in function, or a combination of the two functions. Sensory fibers are axons of sensory ganglia that carry sensory information into the brain and target sensory nuclei. Motor fibers are axons of motor neurons in motor nuclei of the brain stem and target skeletal muscles of the head and neck. Spinal nerves are all mixed nerves with both sensory and motor fibers. Spinal nerves emerge from the spinal cord and reorganize through plexuses, which then give rise to systemic nerves. Thoracic spinal nerves are not part of any plexus, but give rise to the intercostal nerves directly.

Glossary

dorsal (posterior) root ganglion

sensory ganglion attached to the posterior nerve root of a spinal nerve

enteric nervous system

peripheral structures, namely ganglia and nerves, that are incorporated into the digestive system organs

facial nerve

seventh cranial nerve; responsible for contraction of the facial muscles and for part of the sense of taste, as well as causing saliva production

glossopharyngeal nerve

ninth cranial nerve; responsible for contraction of muscles in the tongue and throat and for part of the sense of taste, as well as causing saliva production

olfactory nerve

first cranial nerve; responsible for the sense of smell

optic nerve

second cranial nerve; responsible for visual sensation

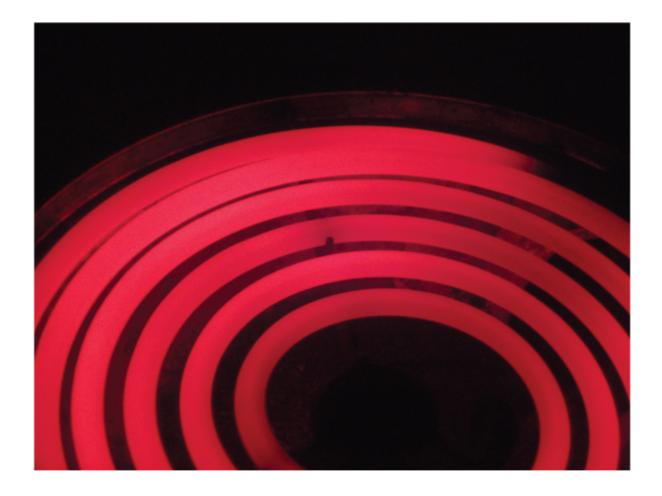
vagus nerve

tenth cranial nerve; responsible for the autonomic control of organs in the thoracic and upper abdominal cavities

OU Human Physiology: Special Senses and Reflexes Introduction class="introduction"

Too Hot to Touch

When high temperatur e is sensed in the skin, a reflexive withdrawal is initiated by the muscles of the arm. Sensory neurons are activated by a stimulus, which is sent to the central nervous system, and a motor response is sent out to the skeletal muscles that control this movement.



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Name the modalities and submodalities of the sensory systems
- Distinguish between the general and special senses
- Compare and contrast the anatomy and mechanisms for each of the special senses and proprioception including brain processing centers
- Explain many disorders of the special senses
- Explain the importance of the thalamus in processing sensory information
- Describe regions of the central nervous system that contribute to somatic functions
- Explain the stimulus-response motor pathway

- Identify the players in a reflex arc and the role of each in a reflex
- Discuss the withdrawal reflex and muscle spindle stretch reflex
- Categorize reflexes

The somatic nervous system is traditionally considered a division within the peripheral nervous system. However, this misses an important point: somatic refers to a functional division, whereas peripheral refers to an anatomic division. The somatic nervous system is responsible for our conscious perception of the environment and for our voluntary responses to that perception by means of skeletal muscles. Peripheral sensory neurons receive input from environmental stimuli, but the neurons that produce motor responses originate in the central nervous system. The distinction between the structures (i.e., anatomy) of the peripheral and central nervous systems and functions (i.e., physiology) of the somatic and autonomic systems can most easily be demonstrated through a simple reflex action. When you touch a hot stove, you pull your hand away. Sensory receptors in the skin sense extreme temperature and the early signs of tissue damage. This triggers an action potential, which travels along the sensory fiber from the skin, through the dorsal spinal root to the spinal cord, and directly activates a ventral horn motor neuron. That neuron sends a signal along its axon to excite the biceps brachii, causing contraction of the muscle and flexion of the forearm at the elbow to withdraw the hand from the hot stove. The withdrawal reflex has more components, such as inhibiting the opposing muscle and balancing posture while the arm is forcefully withdrawn, which will be further explored at the end of this chapter.

The basic withdrawal reflex explained above includes sensory input (the painful stimulus), central processing (the synapse in the spinal cord), and motor output (activation of a ventral motor neuron that causes contraction of the biceps brachii). Expanding the explanation of the withdrawal reflex can include inhibition of the opposing muscle, or cross extension, either of which increase the complexity of the example by involving more central neurons. A collateral branch of the sensory axon would inhibit another ventral horn motor neuron so that the triceps brachii do not contract and slow the withdrawal down. The cross extensor reflex provides a

counterbalancing movement on the other side of the body, which requires another collateral of the sensory axon to activate contraction of the extensor muscles in the contralateral limb.

A more complex example of somatic function is conscious muscle movement. For example, reading of this text starts with visual sensory input to the retina, which then projects to the thalamus, and on to the cerebral cortex. A sequence of regions of the cerebral cortex process the visual information, starting in the primary visual cortex of the occipital lobe, and resulting in the conscious perception of these letters. Subsequent cognitive processing results in understanding of the content. As you continue reading, regions of the cerebral cortex in the frontal lobe plan how to move the eyes to follow the lines of text. The output from the cortex causes activity in motor neurons in the brain stem that cause movement of the eye muscles through cranial nerves. This example also includes sensory input (the retinal projection to the thalamus), central processing (the thalamus and subsequent cortical activity), and motor output (activation of neurons in the brain stem that lead to coordinated contraction of eye muscles).

OU Human Physiology: Sensory Perception By the end of this section, you will be able to:

- Define transduction
- Describe the classification of receptor types
- List the role of each of the following receptors in terms of sensory perception: photoreceptors, exteroreceptors, interoceptors, proprioceptors, chemoreceptors, osmoreceptors, nociceptors, mechanoreceptors, and thermoreceptors
- List the stimuli that each of the special senses detects
- Name the modalities and submodalities of the sensory systems
- Distinguish between the general and special senses
- Describe how gustatory receptor cells respond to chemical stimuli dissolved in the saliva for sweet, sour, and salty foods, how the brain receives these stimuli, and the area of the brain responsible for gustation perception
- Describe the mechanism for olfaction including brain processing centers
- List the structures of the ear that are part of the external, middle, and inner ear
- Describe the pathway for sound conduction from the external ear to the inner ear including transduction of the sound wave into an electrical signal, and the area of the brain responsible for sound perception
- Compare and contrast conduction and sensorineural deafness
- Classify hearing loss as either conduction deafness or sensorineural deafness
- Describe the vestibular apparatus and its role in maintaining equilibrium
- Describe the role of proprioceptors in maintaining balance and coordination and the area of the brain responsible for processing signals from muscle spindles and golgi tendon organs
- List the three major layers of the eye and the associated structures
- Describe the function of the anatomical structures and chambers of the eye
- Define refraction and its importance in vision
- Describe the importance and process of accommodation
- Explain clinical defects in vision to include myopia, hyperopia, emmetropia, astigmatism, presbyopia, cataract, glaucoma, corneal ulcers, and scotopic sensitivity syndrome
- Describe the process of phototransduction in rods

A major role of sensory receptors is to help us learn about the environment around us, or about the state of our internal environment. Stimuli from varying sources, and of different types, are received and changed into the electrochemical signals of the nervous system. This occurs when a stimulus changes the cell membrane potential of a sensory neuron. The stimulus causes the sensory cell to produce an action potential that is relayed into the central nervous system (CNS), where it is integrated with other sensory information—or sometimes higher cognitive functions—to become a conscious perception of that stimulus. The central integration may then lead to a motor response.

Describing sensory function with the term sensation or perception is a deliberate distinction. Sensation is the activation of sensory receptor cells at the level of the stimulus. Perception is the central processing of sensory stimuli into a meaningful pattern. Perception is dependent on sensation, but not all sensations are perceived. Receptors are the cells or structures that detect sensations. A receptor cell is changed directly by a stimulus. A transmembrane protein receptor is a protein in the cell membrane that mediates a physiological change in a neuron, most often through the opening of ion channels or changes in the cell signaling processes. Transmembrane receptors are activated by chemicals called ligands. For example, a molecule in food can serve as a ligand for taste receptors. Other transmembrane proteins, which are not accurately called receptors, are sensitive to mechanical or thermal changes. Physical changes in these proteins increase ion flow across the membrane, and can generate an action potential or a graded potential in the sensory neurons.

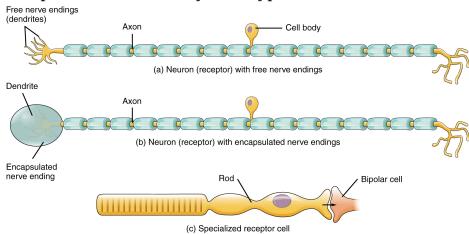
Sensory Receptors

Stimuli in the environment activate specialized receptor cells in the peripheral nervous system. Different types of stimuli are sensed by different types of receptor cells. Receptor cells can be classified into types on the basis of three different criteria: cell type, position, and function. Receptors can be classified structurally on the basis of cell type and their position in relation to stimuli they sense. They can also be classified functionally on the basis of the **transduction** of stimuli, or how the mechanical stimulus, light, or chemical changed the cell membrane potential.

Structural Receptor Types

The cells that interpret information about the environment can be either (1) a neuron that has a **free nerve ending**, with dendrites embedded in tissue that would receive a sensation; (2) a neuron that has an **encapsulated ending** in which the sensory nerve endings are encapsulated in connective tissue that enhances their sensitivity; or (3) a specialized **receptor cell**, which has distinct structural components that interpret a specific type of stimulus ([link]). The pain and temperature receptors in the dermis of the skin are examples of neurons that have free nerve endings. Also located in the dermis of the skin are lamellated corpuscles, neurons with encapsulated nerve endings that respond to pressure and touch. The cells in the retina that respond to light stimuli are an example of a specialized receptor, a **photoreceptor**.

Receptor Classification by Cell Type



Receptor cell types can be classified on the basis of their structure. Sensory neurons can have either (a) free nerve endings or (b) encapsulated endings.

Photoreceptors in the eyes, such as rod cells, are examples of (c) specialized receptor cells. These cells release neurotransmitters onto a bipolar cell, which then synapses with the optic nerve neurons.

Another way that receptors can be classified is based on their location relative to the stimuli. An **exteroceptor** is a receptor that is located near a stimulus in the external environment, such as the somatosensory receptors that are located in the skin. An **interoceptor** is one that interprets stimuli from internal organs and tissues, such as the receptors that sense the increase in blood pressure in

the aorta or carotid sinus. Finally, a **proprioceptor** is a receptor located near a moving part of the body, such as a muscle, that interprets the positions of the tissues as they move.

Functional Receptor Types

A third classification of receptors is by how the receptor transduces stimuli into membrane potential changes. Stimuli are of three general types. Some stimuli are ions and macromolecules that affect transmembrane receptor proteins when these chemicals diffuse across the cell membrane. Some stimuli are physical variations in the environment that affect receptor cell membrane potentials. Other stimuli include the electromagnetic radiation from visible light. For humans, the only electromagnetic energy that is perceived by our eyes is visible light. Some other organisms have receptors that humans lack, such as the heat sensors of snakes, the ultraviolet light sensors of bees, or magnetic receptors in migratory birds.

Receptor cells can be further categorized on the basis of the type of stimuli they transduce. Chemical stimuli can be interpreted by a **chemoreceptor** that interprets chemical stimuli, such as an object's taste or smell. **Osmoreceptors** respond to solute concentrations of body fluids. Additionally, pain is primarily a chemical sense that interprets the presence of chemicals from tissue damage, or similar intense stimuli, through a **nociceptor**. Physical stimuli, such as pressure and vibration, as well as the sensation of sound and body position (balance), are interpreted through a **mechanoreceptor**. Another physical stimulus that has its own type of receptor is temperature, which is sensed through a **thermoreceptor** that is either sensitive to temperatures above (heat) or below (cold) normal body temperature.

Sensory Modalities

Ask anyone what the senses are, and they are likely to list the five major senses —taste, smell, touch, hearing, and sight. However, these are not all of the senses. The most obvious omission from this list is balance. Also, what is referred to simply as touch can be further subdivided into pressure, vibration, stretch, and hair-follicle position, on the basis of the type of mechanoreceptors

that perceive these touch sensations. Other overlooked senses include temperature perception by thermoreceptors and pain perception by nociceptors.

Within the realm of physiology, senses can be classified as either general or specific. A **general sense** is one that is distributed throughout the body and has receptor cells within the structures of other organs. Mechanoreceptors in the skin, muscles, or the walls of blood vessels are examples of this type. General senses often contribute to the sense of touch, as described above, or to **proprioception** (body movement) and **kinesthesia** (body movement), or to a **visceral sense**, which is most important to autonomic functions. A **special sense** is one that has a specific organ devoted to it, namely the eye, inner ear, tongue, or nose.

Each of the senses is referred to as a **sensory modality**. Modality refers to the way that information is encoded, which is similar to the idea of transduction. The main sensory modalities can be described on the basis of how each is transduced. The chemical senses are taste and smell. The general sense that is usually referred to as touch includes chemical sensation in the form of nociception, or pain. Pressure, vibration, muscle stretch, and the movement of hair by an external stimulus, are all sensed by mechanoreceptors. Hearing and balance are also sensed by mechanoreceptors. Finally, vision involves the activation of photoreceptors.

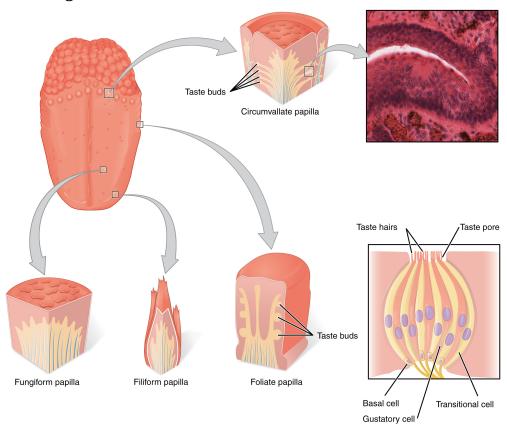
Listing all the different sensory modalities, which can number as many as 17, involves separating the five major senses into more specific categories, or **submodalities**, of the larger sense. An individual sensory modality represents the sensation of a specific type of stimulus. For example, the general sense of touch, which is known as **somatosensation**, can be separated into light pressure, deep pressure, vibration, itch, pain, temperature, or hair movement.

Gustation (Taste)

Only a few recognized submodalities exist within the sense of taste, or **gustation**. Until recently, only four tastes were recognized: sweet, salty, sour, and bitter. Research at the turn of the 20th century led to recognition of the fifth taste, umami, during the mid-1980s. **Umami** is a Japanese word that means "delicious taste," and is often translated to mean savory. Very recent research has suggested that there may also be a sixth taste for fats, or lipids.

Gustation is the special sense associated with the tongue. The surface of the tongue, along with the rest of the oral cavity, is lined by a stratified squamous epithelium. Raised bumps called **papillae** (singular = papilla) contain the structures for gustatory transduction. There are four types of papillae, based on their appearance: circumvallate, foliate, filiform, and fungiform ([link]). Within the structure of the papillae are **taste buds** that contain specialized **gustatory receptor cells** for the transduction of taste stimuli. These receptor cells are sensitive to the chemicals contained within foods that are ingested, and they release neurotransmitters based on the amount of the chemical in the food. Neurotransmitters from the gustatory cells can activate sensory neurons in the facial, glossopharyngeal, and vagus cranial nerves.

The Tongue



The tongue is covered with small bumps, called papillae, which contain taste buds that are sensitive to chemicals in ingested food or drink. Different types of papillae are found in different regions of the tongue. The taste buds contain specialized gustatory receptor cells that respond to chemical stimuli dissolved in the saliva. These receptor cells activate

sensory neurons that are part of the facial and glossopharyngeal nerves. LM \times 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Salty taste is simply the perception of sodium ions (Na⁺) in the saliva ([link]a). When you eat something salty, the salt crystals dissociate into the component ions Na⁺ and Cl⁻, which dissolve into the saliva in your mouth. The Na⁺ concentration becomes high outside the gustatory cells, creating a strong concentration gradient that drives the diffusion of the ion into the cells. The entry of Na⁺ into these cells results in the depolarization of the cell membrane and the generation of a receptor potential.

Sour taste is the perception of H⁺ concentration ([link]b). Just as with sodium ions in salty flavors, these hydrogen ions cross the cell membrane throught the same sodium channels responsible for salty tastes. The influx of hydrogen ions triggers depolarization. Sour flavors are, essentially, the perception of acids in our food. Increasing hydrogen ion concentrations in the saliva (lowering saliva pH) triggers progressively stronger graded potentials in the gustatory cells. For example, orange juice—which contains citric acid—will taste sour because it has a pH value of approximately 3. Of course, it is often sweetened so that the sour taste is masked.

The first two tastes (salty and sour) are triggered by the cations Na⁺ and H⁺. The other tastes (sweet, bitter, and umami) result from food molecules binding to a G protein—coupled receptor. A G protein signal transduction system ultimately leads to depolarization of the gustatory cell. The sweet taste is the sensitivity of gustatory cells to the presence of glucose or sucrose, dissolved in the saliva ([link]c). Other monosaccharides such as fructose, or artificial sweeteners such as aspartame (NutraSweetTM), saccharine, or sucralose (SplendaTM) also activate the sweet receptors. The affinity for each of these molecules varies, and some will taste sweeter than glucose because they bind to the G protein—coupled receptor differently.

Bitter taste is similar to sweet in that food molecules bind to G protein—coupled receptors. However, there are a number of different ways in which this can happen because there are a large diversity of bitter-tasting molecules. Some

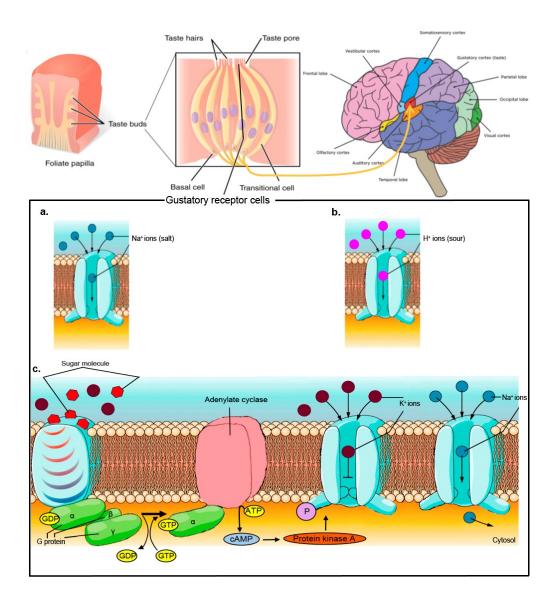
bitter molecules depolarize gustatory cells, whereas others hyperpolarize gustatory cells. Likewise, some bitter molecules increase G protein activation within the gustatory cells, whereas other bitter molecules decrease G protein activation. The specific response depends on which molecule is binding to the receptor.

One major group of bitter-tasting molecules are alkaloids. **Alkaloids** are nitrogen-containing molecules that often have a basic pH. Alkaloids are commonly found in bitter-tasting plant products, such as coffee, hops (in beer), tannins (in wine), tea, and aspirin. By containing toxic alkaloids, the plant is less susceptible to microbe infection and less attractive to herbivores.

Therefore, the function of bitter taste may primarily be related to stimulating the gag reflex to avoid ingesting poisons. Because of this, many bitter foods that are normally ingested are often combined with a sweet component to make them more palatable (cream and sugar in coffee, for example). The highest concentration of bitter receptors appear to be in the posterior tongue, where a gag reflex could still spit out poisonous food.

The taste known as umami is often referred to as the savory taste. Like sweet and bitter, it is based on the activation of G protein—coupled receptors by a specific molecule. The molecule that activates this receptor is the amino acid L-glutamate. Therefore, the umami flavor is often perceived while eating protein-rich foods. Not surprisingly, dishes that contain meat are often described as savory.

Taste Mechanisms



Taste buds on papillae of the tongue are connected to the gustatory cortex. In the membrane of taste hairs are gustatory receptor cells that respond to different chemicals.

(a) Sodium can enter directly through an open sodium channel to depolarize the gustatory cell. (b) Hydrogen ions use the same channel as sodium to depolarize the cell. (c)

Sweet molecules need to use coupling receptors to depolarize the cell (i.e. sucrose uses the cAMP second messenger system to close potassium channels).

Once the gustatory cells are activated by the taste molecules, they release neurotransmitters onto the dendrites of sensory neurons. These neurons are part of the facial and glossopharyngeal cranial nerves, as well as a component within the vagus nerve dedicated to the gag reflex. The facial nerve connects to taste buds in the anterior third of the tongue. The glossopharyngeal nerve connects to taste buds in the posterior two thirds of the tongue. The vagus nerve connects to taste buds in the extreme posterior of the tongue, verging on the pharynx, which are more sensitive to noxious stimuli such as bitterness.

Note:



Go watch this <u>video</u> to learn more about the structure and function of taste receptors.

Note:



Watch this <u>video</u> to learn about Dr. Danielle Reed of the Monell Chemical Senses Center in Philadelphia, Pennsylvania, who became interested in science at an early age because of her sensory experiences. She recognized that her sense of taste was unique compared with other people she knew. Now, she studies the genetic differences between people and their sensitivities to taste stimuli. In the video, there is a brief image of a person sticking out their tongue, which has been covered with a colored dye. This is how Dr. Reed is

able to visualize and count papillae on the surface of the tongue. People fall into two groups known as "tasters" and "non-tasters" based on the density of papillae on their tongue, which also indicates the number of taste buds. Non-tasters can taste food, but they are not as sensitive to certain tastes, such as bitterness. Dr. Reed discovered that she is a non-taster, which explains why she perceived bitterness differently than other people she knew. Are you very sensitive to tastes? Can you see any similarities among the members of your family?

Olfaction (Smell)

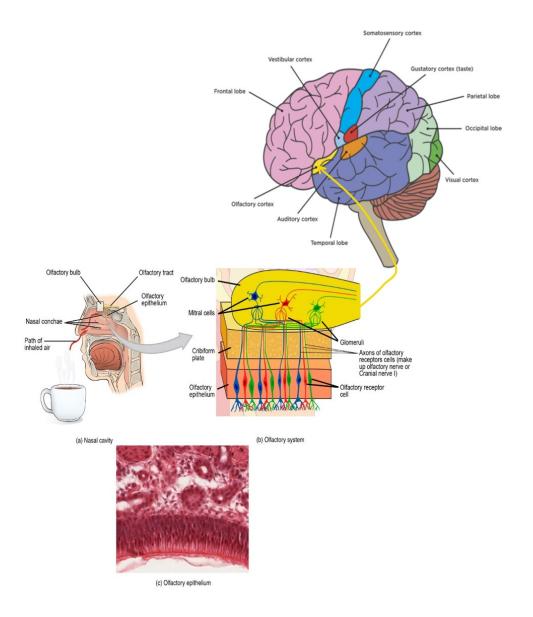
Like taste, the sense of smell, or **olfaction**, is also responsive to chemical stimuli. The olfactory receptor neurons are bipolar sensory neurons located in a small region referred to as the **olfactory epithelium** ([link]). Each **olfactory receptor neuron** has dendrites that extend from the apical surface of the epithelium into the mucus lining the cavity. As airborne molecules are inhaled through the nose, they pass over the olfactory epithelial region and dissolve into the mucus. These **odorant molecules** bind to proteins that keep them dissolved in the mucus and help transport them to the olfactory dendrites. The odorant–protein complex binds to a receptor protein within the cell membrane of an olfactory dendrite. These receptors are G protein-coupled, and will activate the cAMP second messenger. In olfaction receptor cells, cAMP binds to cation channels. These cation channels open allowing both sodium and calcium influx. The calcium ion influx also causes chloride channels to open and chloride efflux occurs. This increases depolarization of the olfactory receptors. This influx of positive ions and efflux of negative ions causes the membrane to depolarize. If depolarization of the membrane causes threshold to be reached, an action potential will be generated on the axon of the olfactory receptor neuron.

The axon of an olfactory neuron make up the olfactory nerve (cranial nerve I). The axons extend from the basal surface of the epithelium, through an olfactory foramen in the cribriform plate of the ethmoid bone, and into the brain. This group of axons is called the olfactory tract and connects to the **olfactory bulb** on the frontal lobe in the brain. Here, the olfactory nerve communicates with second-order neurons called mitral cells. Since many olfactory nerves synapse with a single mitral cell, this region is called the

glomeruli. From there, the axons split to travel to several brain regions. Some travel to the cerebrum, specifically to the primary olfactory cortex for perception and discrimination of smell. Others project to structures within the limbic system and hypothalamus, where smells become associated with long-term memory and emotional responses. This is how certain smells trigger emotional memories, such as the smell of food associated with one's birthplace. Smell is the one sensory modality that does not synapse in the thalamus before connecting to the cerebral cortex. This intimate connection between the olfactory system and the cerebral cortex is one reason why smell can be a potent trigger of memories and emotion.

The nasal epithelium, including the olfactory cells, can be harmed by airborne toxic chemicals. Therefore, the olfactory neurons are regularly replaced within the nasal epithelium, after which the axons of the new neurons must find their appropriate connections in the olfactory bulb. These new axons grow along the axons that are already in place in the cranial nerve.

The Olfactory System



(a) The olfactory system begins in the peripheral structures of the nasal cavity. (b) The olfactory receptor neurons are within the olfactory epithelium and transmits action potentials to the olfactory complex in the brain.

(source: Chabacano:Wikimedia) (c) Axons of the olfactory receptor neurons project through the cribriform plate of the ethmoid bone and synapse with the neurons of the olfactory bulb (tissue source: simian). LM × 812. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:

Disorders of the...

Olfactory System: Anosmia

Blunt force trauma to the face, such as that common in many car accidents, can lead to the loss of the olfactory nerve, and subsequently, loss of the sense of smell. This condition is known as **anosmia**. When the frontal lobe of the brain moves relative to the ethmoid bone, the olfactory tract axons may be sheared apart. Professional fighters often experience anosmia because of repeated trauma to face and head. In addition, certain pharmaceuticals, such as antibiotics, can cause anosmia by killing all the olfactory neurons at once. If no axons are in place within the olfactory nerve, then the axons from newly formed olfactory neurons have no guide to lead them to their connections within the olfactory bulb. There are temporary causes of anosmia, as well, such as those caused by inflammatory responses related to respiratory infections or allergies.

Loss of the sense of smell can result in food tasting bland. A person with an impaired sense of smell may require additional spice and seasoning levels for food to be tasted. Anosmia may also be related to some presentations of mild depression, because the loss of enjoyment of food may lead to a general sense of despair.

The ability of olfactory neurons to replace themselves decreases with age, leading to age-related anosmia. This explains why some elderly people salt their food more than younger people do. However, this increased sodium intake can increase blood volume and blood pressure, increasing the risk of cardiovascular diseases in the elderly.

Note:

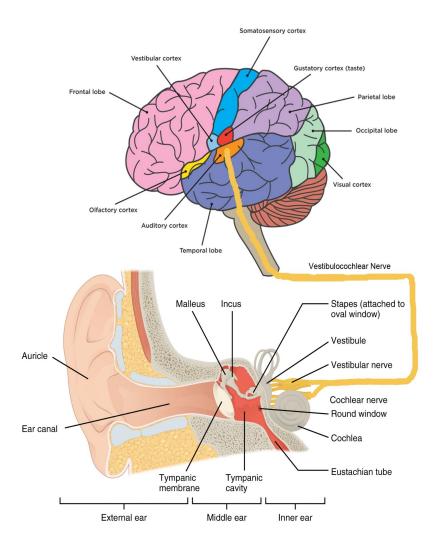


Go watch this <u>video</u> to learn more about the function and structure of the olfaction system.

Audition (Hearing)

Hearing, or **audition**, is the transduction of sound waves into a neural signal that is made possible by the structures of the ear ([link]). The large, fleshy structure on the lateral aspect of the head is known as the **auricle**. Some sources will also refer to this structure as the pinna, though that term is more appropriate for a structure that can be moved, such as the external ear of a cat. The C-shaped curves of the auricle direct sound waves toward the ear and into the ear canal which is also called the external auditory meatus. The canal is embedded in the temporal bone. At the end of the auditory canal is the tympanic membrane, or ear drum, which vibrates after it is struck by sound waves. The auricle, ear canal, and tympanic membrane are often referred to as the **external ear**. The **middle ear** consists of a space spanned by three small bones called the **ossicles**. The three ossicles are the **malleus**, **incus**, and **stapes**, which are Latin names that roughly translate to hammer, anvil, and stirrup. The malleus is attached to the tympanic membrane and articulates with the incus. The incus, in turn, articulates with the stapes. The stapes is then attached to the **inner ear**, where the sound waves will be transduced into a neural signal. The ossicles play a very important role in sound wave amplification. The middle ear is connected to the pharynx through the Eustachian tube, which helps equilibrate air pressure across the tympanic membrane. The tube is normally closed but will pop open when the muscles of the pharynx contract during swallowing or yawning.

The Auditory System



The external ear contains the auricle, ear canal, and tympanic membrane. The middle ear contains the ossicles and is connected to the pharynx by the Eustachian tube. The inner ear contains the cochlea and vestibule, which are responsible for audition and equilibrium, respectively. The vestibulocochlear nerve goes to the auditory cortex of the temporal lobe in the brain.

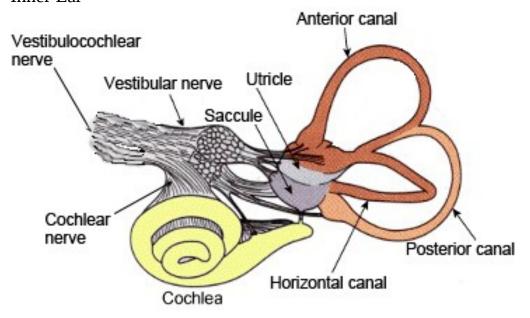
Note:



Watch this <u>video</u> to learn about sound and hearing.

The inner ear is often described as a bony labyrinth, as it is composed of a series of canals embedded within the temporal bone. It has two separate regions, the **cochlea** and the **vestibule**, which are responsible for hearing and balance, respectively. The neural signals from these two regions are relayed to the brain stem through separate fiber bundles. However, these two distinct bundles travel together from the inner ear to the brain stem as the vestibulocochlear nerve (cranial nerve VIII)([link]). Sound is transduced into neural signals within the cochlear region of the inner ear to the auditory cortex in the brain.

Inner Ear

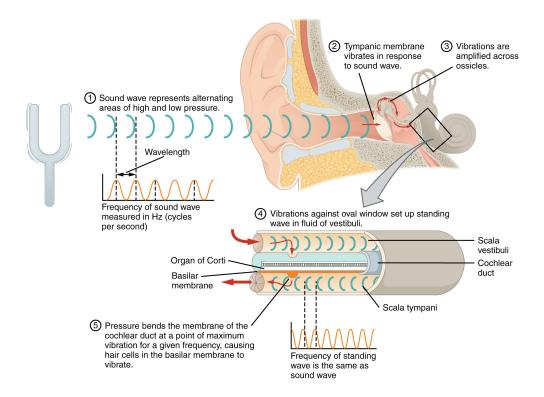


The inner ear is comprised of the cochlear which contains

the receptor for hearing as well as the utricle, saccule, and three semicircular canals which are used to maintain balance (modified from: Thomas.haslwanter: Wikipedia). The cochlear nerve receives input from the cochlea while the vestibular nerve receives input from the saccule, utricle, and semicircular canals. The cochlear and vestibular nerves will merge to form the vestibulocochlear nerve.

The oval window is located at the beginning of a fluid-filled tube within the cochlea called the **scala vestibuli**. The scala vestibuli extends from the oval window, travelling above the **cochlear duct**, which is the central cavity of the cochlea that contains the sound-transducing neurons. At the uppermost tip of the cochlea, the scala vestibuli curves over the top of the cochlear duct. The fluid-filled tube, now called the **scala tympani**, returns to the base of the cochlea, this time travelling under the cochlear duct. The scala tympani ends at the **round window**, which is covered by a membrane that contains the fluid within the scala. As vibrations of the ossicles travel through the oval window, the fluid of the scala vestibuli and scala tympani moves in a wave-like motion. The frequency of the fluid waves match the frequencies of the sound waves ([link]). The membrane covering the round window will bulge out or pucker in with the movement of the fluid within the scala tympani.

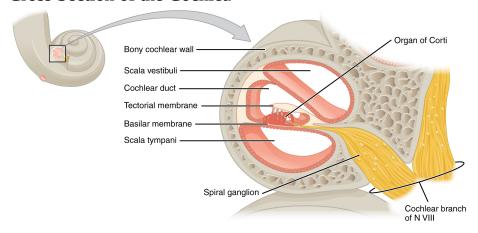
Transmission of Sound Waves to Cochlea



A sound wave causes the tympanic membrane to vibrate. This vibration is amplified as it moves across the malleus, incus, and stapes. The amplified vibration is picked up by the oval window causing pressure waves in the fluid of the scala vestibuli and scala tympani. The complexity of the pressure waves is determined by the changes in amplitude and frequency of the sound waves entering the ear.

A cross-sectional view of the cochlea shows that the scala vestibuli and scala tympani run along both sides of the cochlear duct ([link]). The cochlear duct contains several **organs of Corti**, which tranduce the wave motion of the two scala into neural signals. The organs of Corti lie on top of the **basilar membrane**, which is the side of the cochlear duct located between the organs of Corti and the scala tympani ([link]). As the fluid waves move through the scala vestibuli and scala tympani, the basilar membrane moves at a specific spot, depending on the frequency of the waves. Higher frequency waves move the region of the basilar membrane that is close to the base of the cochlea. Lower frequency waves move the region of the basilar membrane that is near the tip of the cochlea.

Cross Section of the Cochlea

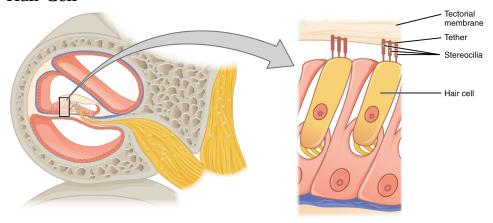


The three major spaces within the cochlea are highlighted. The scala tympani and scala vestibuli lie on either side of the cochlear duct. The organ of Corti, containing the mechanoreceptor hair cells, is adjacent to the scala tympani, where it sits atop the basilar membrane.

The organs of Corti contain **hair cells**, which are named for the hair-like **stereocilia** extending from the cell's apical surfaces ([link]). The stereocilia are an array of microvilli-like structures arranged from tallest to shortest. The tallest stereocilia is called the **kinocilium**. These sterocilia are embedded into the **tectorial membrane** which is attached medially to the organ of Corti ([link]). Protein fibers, called **tip links** tether adjacent hairs together within each array, such that the stereocilia will bend in response to movements of the basilar membrane. When the pressure waves from the scala move the basilar membrane, the tectorial membrane slides across the stereocilia. This bends the stereocilia either toward or away from the kinocilium of each array. When the stereocilia bend toward the kinocilium, tension in the protein tethers open potassium ion channels in the hair cells membrane and potassium influx occurs due to the higher potassium concentration outside the stereocilia and the lower potassium concentration in the stereocilia. This influx will depolarize the hair cells causing voltage-gated calcium channels to open on the hair cell and calcium influx. The calcium influx will cause exocytosis of neurotransmitters which will bind to ligand gated channels on the afferent cochlear nerve fibers,

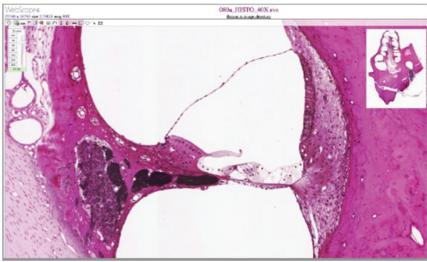
triggering nerve impulses that travel down the afferent nerve fibers. When the stereocilia bend away from the kinocilium, the tension on the tethers slackens and the potassium ion channels close. When no sound is present, and the stereocilia are standing straight, a small amount of tension still exists on the tethers, keeping the membrane potential of the hair cell slightly depolarized ([link]).

Hair Cell



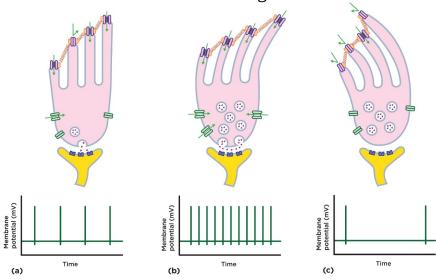
The hair cell is a mechanoreceptor with an array of stereocilia emerging from its apical surface. The stereocilia are tethered together by proteins that open ion channels when the array is bent toward the tallest member of their array, and closed when the array is bent toward the shortest member of their array.

Cochlea and Organ of Corti



LM × 412. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)





Stereocilia are used for hearing. When the pressure waves from the scala move the basilar membrane, the tectorial membrane slides across the stereocilia. This bends the stereocilia either toward or away from the kinocilium of each array which will either depolarize or hyperpolarize the hair cell which will then travel to the afferent cochlear nerve fibers.

When the neurotransmitters are released from the hair cells and they bind to the receptors on the cochlear nerve, the action potential that results will travel via the cochlear nerve which ultimately fuses with the vestibular nerve to for the vestibulocochlear nerve (cranial nerve VIII). Signals from this nerve travel through the thalamus on their way to the auditory cortex in the temporal lobe to perceive sound.

Note:



Go watch this <u>video</u> to learn more about sound and hearing. NOTE: Kinocilium only refers to the tallest stereocilium and not all the hair cells.

Note:

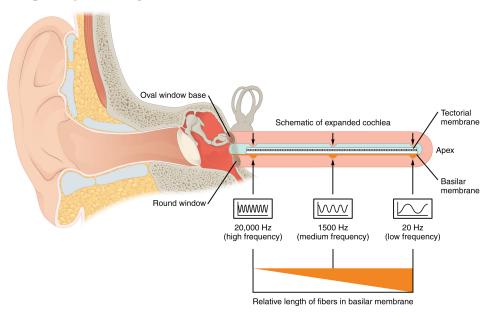


View the University of Michigan WebScope at http://virtualslides.med.umich.edu/Histology/Central%20Nervous%20System/080a_HISTO_40X.svs/view.apml to explore the tissue sample in greater detail. The basilar membrane is the thin membrane that extends from the central core of the cochlea to the edge. What is anchored to this membrane so that they can be activated by movement of the fluids within the cochlea?

As stated above, a given region of the basilar membrane will only move if the incoming sound is at a specific frequency. Because the tectorial membrane only moves where the basilar membrane moves, the hair cells in this region will also only respond to sounds of this specific frequency. Therefore, as the frequency of a sound changes, different hair cells are activated all along the basilar membrane. The cochlea encodes auditory stimuli for frequencies between 20 and 20,000 Hz, which is the range of sound that human ears can detect. The unit of Hertz measures the frequency of sound waves in terms of cycles produced per second. Frequencies as low as 20 Hz are detected by hair

cells at the apex, or tip, of the cochlea. Frequencies in the higher ranges of 20 KHz are encoded by hair cells at the base of the cochlea, close to the round and oval windows ([link]). Most auditory stimuli contain a mixture of sounds at a variety of frequencies and intensities (represented by the amplitude of the sound wave). The hair cells along the length of the cochlear duct, which are each sensitive to a particular frequency, allow the cochlea to separate auditory stimuli by frequency, just as a prism separates visible light into its component colors.

Frequency Coding in the Cochlea



The standing sound wave generated in the cochlea by the movement of the oval window deflects the basilar membrane on the basis of the frequency of sound. Therefore, hair cells at the base of the cochlea are activated only by high frequencies, whereas those at the apex of the cochlea are activated only by low frequencies.

Note:			



Watch this <u>video</u> to learn more about how the structures of the ear convert sound waves into a neural signal by moving the "hairs," or stereocilia, of the cochlear duct. Specific locations along the length of the duct encode specific frequencies, or pitches. The brain interprets the meaning of the sounds we hear as music, speech, noise, etc. Which ear structures are responsible for the amplification and transfer of sound from the external ear to the inner ear?

Note:



Watch this <u>animation</u> to learn more about the inner ear and to see the cochlea unroll, with the base at the back of the image and the apex at the front. Specific wavelengths of sound cause specific regions of the basilar membrane to vibrate, much like the keys of a piano produce sound at different frequencies. Based on the animation, where do frequencies—from high to low pitches—cause activity in the hair cells within the cochlear duct?

Note:



Equilibrium (Balance)

Along with audition, the inner ear is responsible for encoding information about **equilibrium**, the sense of balance. This system for maintaining balance is called the vestibular system. It is located within the vestibule of the inner ear and consists of five distinct structures, three semicircular canals, the saccule, and the utricle. The **semicircular canals** detect dynamic movements (i.e. angular accelerations such as head rotation), while the two otolith organs, the **saccule** and **utricle** that detect linear accelerations and head position (see [link]). The utricle is sensitive to horizontal movements while the saccule is sensitive to vertical movements. The receptor for equilibrium is similar to the mechanoreceptor for hearing—a hair cell with stereocilia—senses head position, head movement, and whether our bodies are in motion. The neural signals generated in the **vestibular nerve** are transmitted through the vestibulocochlear nerve to the brain stem and cerebellum.

The utricle and saccule are both largely composed of **macula** tissue (plural = maculae). The maculae are sensory receptors for linear acceleration and head position. The macula is composed of hair cells surrounded by support cells. The stereocilia of the hair cells extend into a viscous gel called the **otolith** ([link]). The otolith contains calcium carbonate crystals, making it denser and giving it greater inertia than the macula. Therefore, gravity will cause the otolith to move separately from the macula in response to head movements. Tilting the head causes the otolith to slide over the macula in the direction of gravity. The moving otolith layer, in turn, bends the sterocilia to cause some hair cells to depolarize as others hyperpolarize ([link]). The exact tilt of the head is interpreted by the brain on the basis of the pattern of hair-cell depolarization.

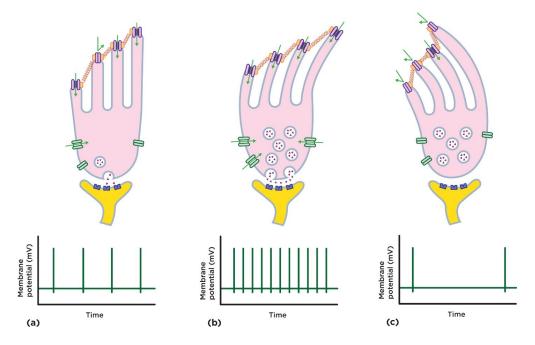
The utricle can detect horizontal movements and head position because the maculae are oriented on a horizontal plane. The maculae for the saccule are oriented on a vertical plane and therefore detect vertical movements and head position. Hence, the mechanism for maculae in both the utricle and saccule is the same, the difference only being the orientation of the maculae which therefore results with either horizontal or vertical movement.

Linear Acceleration Coding by Maculae a. Head neutral position b. Utricle (cut) Saccule Kinocillum Otolith Hair cell Gelatinous layer Accelerating forward C. Afferent of the vestibular nerve

The maculae are specialized for sensing linear acceleration, such as when gravity acts on the tilting head, or if the head starts moving in a straight line. The difference in inertia between the hair cell stereocilia and the otolith in which they are embedded leads to a shearing force that causes the stereocilia to bend in the direction of that linear acceleration.

Head tilted forward

The Role of Stereocilia in Equilibrium

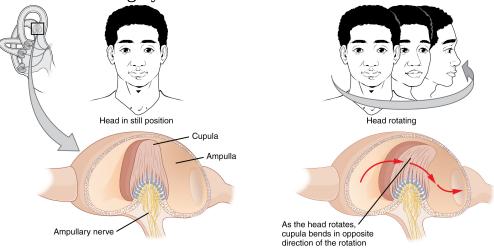


Stereocilia are used for hearing and equilibrium. (a.) While the head is in a neutral position, constant motion or at rest, the stereocilia are erect, with some depolarization occurring, and some action potentials being generated along the vestibular nerve. (b.) While the head is acceleration forward, the otoliths push down on the gelatinous matrix causing the stereocilia to bend in the opposite direction of the acceleration and toward kinocilium. This increases depolarization of stereocilia and ultimately increases the frequency of action potentials on the vestibular nerve. (c.) When the head tilts forward the otoliths are pushed forward due to gravity which pulls on the gelatinous material bending the stereocilia away from the kinocilium resulting in hyperpolarization and fewer action potentials in the vestibular nerve fiber.

The semicircular canals are three ring-like extensions of the vestibule that detect rotational acceleration. One canal is oriented in the horizontal plane, whereas the other two canals are oriented in the vertical plane. The anterior and posterior vertical canals are oriented at approximately 45 degrees relative to the sagittal plane ([link]). Each of the semicircular canals helps monitor

different rotational movements. The lateral semicircular canal monitors spinning or when shaking head left to right to indicate "no." The posterior semicircular canal monitors rotation when you tilt your head ear to ear or while doing a cartwheel. Finally, the anterior semicircular canal monitors forward and backwards nodding of the head to indicate "yes" or when performing a somersault. The base of each semicircular canal, where it meets with the vestibule, connects to an enlarged region known as the **ampulla**. The ampulla contains the hair cells that respond to the rotational movement. The stereocilia of these hair cells extend into the **cupula**, a membrane that attaches to the top of the ampulla. As the head rotates in a plane parallel to the semicircular canal, the fluid lags, deflecting the cupula in the direction opposite to the head movement. The semicircular canals contain several ampullae, with some oriented horizontally and others oriented vertically. By comparing the relative movements of both the horizontal and vertical ampullae, the vestibular system can detect the direction of most head movements within three-dimensional (3-D) space by sending action potentials along the vestibular nerve to the vestibulocochlear nerve (cranial nerve VIII) and then on to primarily to the cerebellum for equilibrium processing or through the thalamus and to the cerebral cortex, but most integration occurs in the cerebellum.

Rotational Coding by Semicircular Canals



Rotational movement of the head is encoded by the hair cells in the base of the semicircular canals. As one of the canals moves in an arc with the head, the internal fluid moves in the opposite direction, causing the cupula and stereocilia to bend. The movement of two canals within a plane results in information about the direction in which the

head is moving, and activation of all six canals can give a very precise indication of head movement in three dimensions.

Somatosensation (Touch)

Somatosensation is considered a general sense, as opposed to the special senses discussed in this section. Somatosensation is the group of sensory modalities that are associated with touch, proprioception, and interoception. These modalities include pressure, vibration, light touch, tickle, itch, temperature, pain, proprioception, and kinesthesia. This means that its receptors are not associated with a specialized organ, but are instead spread throughout the body in a variety of organs. Many of the somatosensory receptors are located in the skin, but receptors are also found in muscles, tendons, joint capsules, ligaments, and in the walls of visceral organs.

Two types of somatosensory signals that are transduced by free nerve endings are pain and temperature. These two modalities use thermoreceptors and nociceptors to transduce temperature and pain stimuli, respectively. Temperature receptors are stimulated when local temperatures differ from body temperature. Some thermoreceptors are sensitive to just cold and others to just heat. Nociception is the sensation of potentially damaging stimuli. Mechanical, chemical, or thermal stimuli beyond a set threshold will elicit painful sensations. Stressed or damaged tissues release chemicals that activate receptor proteins in the nociceptors. For example, the sensation of heat associated with spicy foods involves **capsaicin**, the active molecule in hot peppers. Capsaicin molecules bind to a transmembrane ion channel in nociceptors that is sensitive to temperatures above 37°C. The dynamics of capsaicin binding with this transmembrane ion channel is unusual in that the molecule remains bound for a long time. Because of this, it will decrease the ability of other stimuli to elicit pain sensations through the activated nociceptor. For this reason, capsaicin can be used as a topical analgesic, such as in products such as Icy HotTM.

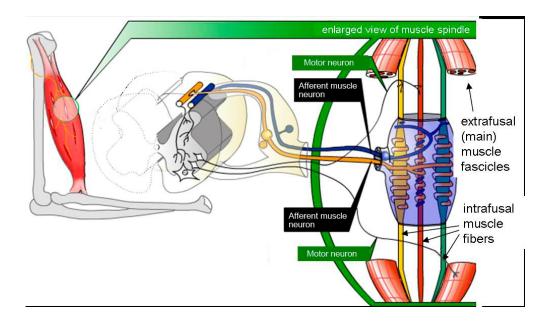
If you drag your finger across a textured surface, the skin of your finger will vibrate. Such low frequency vibrations are sensed by mechanoreceptors called

Merkel cells, also known as type I cutaneous mechanoreceptors. Merkel cells are located in the stratum basale of the epidermis. Deep pressure and vibration is transduced by lamellated (Pacinian) corpuscles, which are receptors with encapsulated endings found deep in the dermis, or subcutaneous tissue. Light touch is transduced by the encapsulated endings known as tactile (Meissner) corpuscles. Follicles are also wrapped in a plexus of nerve endings known as the hair follicle plexus. These nerve endings detect the movement of hair at the surface of the skin, such as when an insect may be walking along the skin. Stretching of the skin is transduced by stretch receptors known as bulbous corpuscles. Bulbous corpuscles are also known as Ruffini corpuscles, or type II cutaneous mechanoreceptors.

Other somatosensory receptors called proprioreceptors are found in skeletal muscle, joint capsules, and ligaments ([link]). These receptors monitor the stretching of tendons, muscles, and the components of joints to monitor body position in space and body parts relative to one another. For example, have you ever stretched your muscles before or after exercise and noticed that you can only stretch so far before your muscles spasm back to a less stretched state? This spasm is a reflex that is initiated by proprioreceptors to avoid muscle tearing. Such receptors can also prevent over-contraction of a muscle. In skeletal muscle tissue, these stretch receptors are called muscle spindles. Muscle spindles are an extension of dendrites of sensory neurons that are buried among the extrafusal fibers of the skeletal muscle. Golgi tendon organs consist of sensory nerve endings intermingled among collagen fibers in tendons. When the muscle spindle or Golgi tendon senses stretch it excites these receptors which sends electrical signals to the cerebellum for interpretation and primary somatic sensory cortex on the frontal lobe.

Skeletal muscles often work in antagonistic pairs to perform movements. For instance, when the bicep contracts to bend the arm at the elbow, the tricep must relax to allow the movement. As the bicep shortens, the proprioceptors in the bicep send fewer signals to the brain. In contrast, as the tricep relaxes in the same movement, the muscle elongates which triggers the muscle spindles to send a larger signal to the brain. This differential input from the two muscles, give the brain information that can be used to sense the position of the arm in space. Then, the signals are reversed to straighten the arm, because the tricep must contract and the bicep must relax. The types of nerve endings, their locations, and the stimuli they transduce are presented in [link].

Proprioreceptors



Proprioreceptors are found in skeletal muscles, joint capsules, and ligaments. One type of proprioreceptor is the muscle spindle found within skeletal. Muscle spindles send information to the brain about muscle length and therefore body position. (credit: Neuromechanics/ Wikimedia)

Mechanoreceptors of Somatosensation				
Name	Historical (eponymous) name	Location(s)	Stimuli	

Mechanoreceptors of Somatosensation				
Name	Historical (eponymous) name	Location(s)	Stimuli	
Free nerve endings	*	Dermis, cornea, tongue, joint capsules, visceral organs	Pain, temperature mechanical deformation	
Mechanoreceptors	Merkel's discs	Epidermal— dermal junction, mucosal membranes	Low frequency vibration (5–15 Hz)	
Tactile corpuscle	Meissner's corpuscle	Papillary dermis, especially in the fingertips and lips	Light touch, vibrations below 50 Hz	
Lamellated corpuscle	Pacinian corpuscle	Deep dermis, subcutaneous tissue	Deep pressure, high-frequency vibration (around 250 Hz)	
Hair follicle plexus	*	Wrapped around hair follicles in	Movement of hair	

the dermis

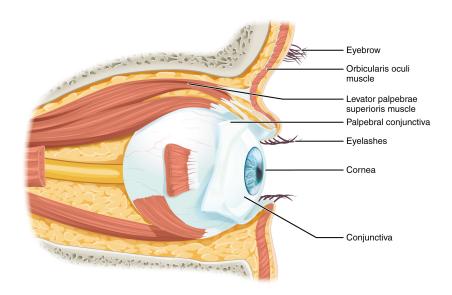
Mechanoreceptors of Somatosensation					
Name	Historical (eponymous) name	Location(s)	Stimuli		
Muscle spindle	*	In line with skeletal muscle fibers	Muscle contraction and stretch		
Tendon stretch organ	Golgi tendon organ	In line with tendons	Stretch of tendons		

^{*}No corresponding eponymous name.

Vision

Vision is the special sense of sight that is based on the transduction of light stimuli received through the eyes. The eyes are located within either orbit in the skull. The bony orbits surround the eyeballs, protecting them and anchoring the soft tissues of the eye ([link]). The eyelids, with lashes at their leading edges, help to protect the eye from abrasions by blocking particles that may land on the surface of the eye. The inner surface of each lid is a thin membrane known as the **conjunctiva**. The conjunctiva extends over the white areas of the eye (the sclera), connecting the eyelids to the eyeball. Tears are produced by the **lacrimal gland**, located beneath the lateral edges of the nose. Tears produced by this gland flow through the **lacrimal duct** to the medial corner of the eye, where the tears flow over the conjunctiva, washing away foreign particles.

The Eye in the Orbit

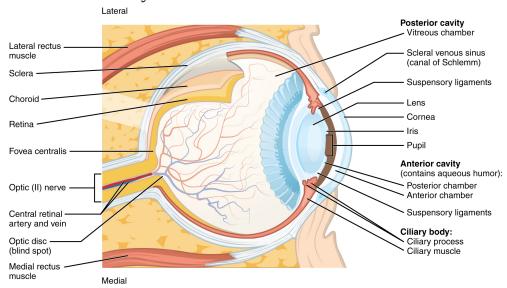


The eye is located within the orbit and surrounded by soft tissues that protect and support its function. The orbit is surrounded by cranial bones of the skull.

The eye itself is a hollow sphere composed of three layers of tissue. The outermost layer is the **sclera**, which is the white of the eye. The anterior region of the sclera is the translucent **cornea** that allows light to enter the eye. The sclera accounts for five sixths of the surface of the eye, most of which is not visible, though humans are unique compared with many other species in having so much of the "white of the eye" visible ([link]). The middle layer of the eye is mostly composed of the choroid, ciliary body, and iris. The **choroid** is a layer of highly vascularized connective tissue that provides a blood supply to the eyeball. The choroid is posterior to the **ciliary body**, a muscular structure that is attached to the **lens** by **zonular fibers** (often called suspensory ligaments). These two structures allow the lens to bulge or flatten in order to focus light on the back of the eye. Overlaying the ciliary body, and visible in the anterior eye, is the **iris**—the colored part of the eye. The iris is a smooth muscle that opens or closes the **pupil**, which is the hole at the center of the eye that allows light to enter. The iris constricts the pupil in response to bright light and dilates the pupil in response to dim light. The innermost layer of the eye is the **neural tunic**, or **retina**, which contains the nervous tissue responsible for photoreception.

The eye is also divided into two cavities: the anterior cavity and the posterior cavity. The anterior cavity is the space between the cornea and lens, including the iris and ciliary body. It is filled with a watery fluid called the **aqueous humor**. The posterior cavity is the space behind the lens that extends to the posterior side of the interior eyeball, where the retina is located. The posterior cavity is filled with a more viscous fluid called the **vitreous humor**.

Structure of the Eye



The sphere of the eye can be divided into anterior and posterior chambers. The wall of the eye is composed of three layers: the fibrous tunic, vascular tunic, and neural tunic. Within the neural tunic is the retina, with three layers of cells and two synaptic layers in between. The center of the retina has a small indentation known as the fovea.

Note:



Watch this <u>video</u> to learn more about the structure of the eye.

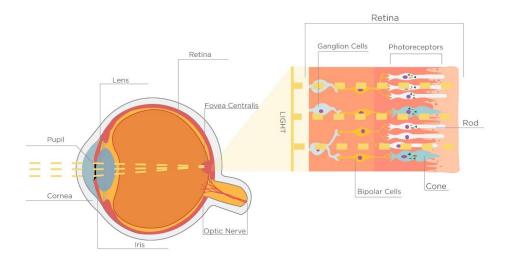
Note:



Watch this <u>video</u> to get an overview of vision.

The retina is composed of several layers and contains specialized cells for the initial processing of visual stimuli. The photoreceptors (rods and cones) change their membrane potential when stimulated by light energy. The change in membrane potential alters the amount of neurotransmitter that the photoreceptor cells release onto **bipolar cells** in the **outer layer of the retina**. It is the bipolar cell in the retina that connects a photoreceptor to a **retinal ganglion cell (RGC)** in the **inner layer of the retina**. There, **amacrine cells** additionally contribute to retinal processing before an action potential is produced by the RGC. The axons of RGCs, which lie at the innermost layer of the retina, collect at the **optic disc** and leave the eye as the **optic nerve** (see [link]). Because these axons pass through the retina, there are no photoreceptors at the very back of the eye, where the optic nerve begins. This creates a "blind spot" in the retina, and a corresponding blind spot in our visual field ([link]).

Retina and Optic Disc

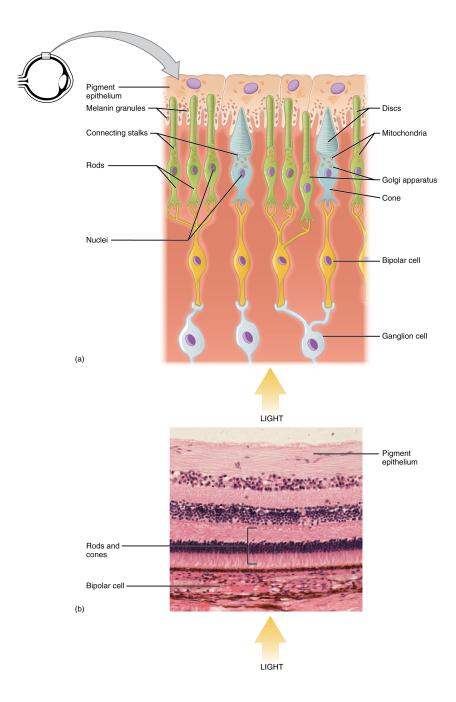


The configuration of the optic disc and retina in the eye which causes the blind spot within the visual field.

At the exact center of the retina is a small area known as the **fovea**. At the fovea, the retina lacks the supporting cells and blood vessels, and only contains photoreceptors. Therefore, **visual acuity**, or the sharpness of vision, is greatest at the fovea. This is because the fovea is where the least amount of incoming light is absorbed by other retinal structures (see [link]). As one moves in either direction from this central point of the retina, visual acuity drops significantly. In addition, each photoreceptor cell of the fovea is connected to a single RGC. Therefore, this RGC does not have to integrate inputs from multiple photoreceptors, which reduces the accuracy of visual transduction. Toward the edges of the retina, several photoreceptors converge on RGCs (through the bipolar cells) up to a ratio of 50 to 1. The difference in visual acuity between the fovea and peripheral retina is easily evidenced by looking directly at a word in the middle of this paragraph. The visual stimulus in the middle of the field of view falls on the fovea and is in the sharpest focus. Without moving your eyes off that word, notice that words at the beginning or end of the paragraph are not in focus. The images in your peripheral vision are focused by the peripheral retina, and have vague, blurry edges and words that are not as clearly identified. As a result, a large part of the neural function of the eyes is concerned with moving the eyes and head so that important visual stimuli are centered on the fovea.

Light falling on the retina causes chemical changes to pigment molecules in the photoreceptors, ultimately leading to a change in the activity of the RGCs. Photoreceptor cells have two parts, the **inner segment** and the **outer segment** ([link]). The inner segment contains the nucleus and other common organelles of a cell, whereas the outer segment is a specialized region in which photoreception takes place. There are two types of photoreceptors—rods and cones—which differ in the shape of their outer segment. The rod-shaped outer segments of the **rod photoreceptor** contain a stack of membrane-bound discs that contain the photosensitive pigment **rhodopsin**. The cone-shaped outer segments of the **cone photoreceptor** contain their photosensitive pigments in infoldings of the cell membrane. There are three cone photopigments, called **opsins**, which are each sensitive to a particular wavelength of light. The wavelength of visible light determines its color. The pigments in human eyes are specialized in perceiving three different primary colors: red, green, and blue.

Photoreceptor



(a) All photoreceptors have inner segments containing the nucleus and other important organelles and outer segments with membrane arrays containing the photosensitive opsin molecules. Rod outer segments are long columnar shapes with stacks of membrane-bound discs that contain the rhodopsin pigment. Cone outer segments are short, tapered shapes with folds of

membrane in place of the discs in the rods. (b)
Tissue of the retina shows a dense layer of nuclei
of the rods and cones. LM × 800. (Micrograph
provided by the Regents of University of Michigan
Medical School © 2012)

Note:



Go watch this <u>video</u> to learn more about photoreceptors and the differences between rods and cones.

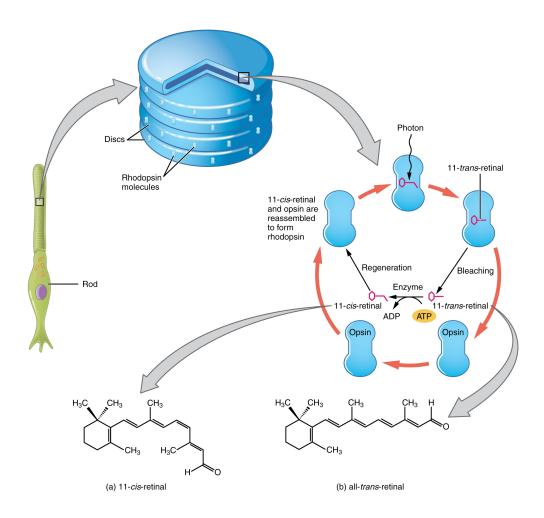
At the molecular level, visual stimuli cause changes in the photopigment molecule that lead to changes in membrane potential of the photoreceptor cell. A single unit of light is called a **photon**, which is described in physics as a packet of energy with properties of both a particle and a wave. The energy of a photon is represented by its wavelength, with each wavelength of visible light corresponding to a particular color. Visible light is electromagnetic radiation with a wavelength between 380 and 720 nm. Longer wavelengths of less than 380 nm fall into the infrared range, whereas shorter wavelengths of more than 720 nm fall into the ultraviolet range. Light with a wavelength of 380 nm is blue whereas light with a wavelength of 720 nm is dark red. All other colors fall between red and blue at various points along the wavelength scale.

Opsin pigments are actually transmembrane proteins that contain a cofactor known as **retinal**. Retinal is a hydrocarbon molecule related to vitamin A. When a photon hits retinal, the long hydrocarbon chain of the molecule is biochemically altered. Specifically, photons cause some of the double-bonded

carbons within the chain to switch from a *cis* to a *trans* conformation. This process is called **photoisomerization**. Before interacting with a photon, retinal's flexible double-bonded carbons are in the *cis* conformation. This molecule is referred to as 11-*cis*-retinal. A photon interacting with the molecule causes the flexible double-bonded carbons to change to the *trans*-conformation, forming all-*trans*-retinal, which has a straight hydrocarbon chain ([link]).

The shape change of retinal in the photoreceptors initiates visual transduction in the retina. Activation of retinal and the opsin proteins result in activation of a G protein. The G protein changes the membrane potential of the photoreceptor cell, which then releases less neurotransmitter into the outer synaptic layer of the retina. Until the retinal molecule is changed back to the 11-cis-retinal shape, the opsin cannot respond to light energy, which is called bleaching. When a large group of photopigments is bleached, the retina will send information as if opposing visual information is being perceived. After a bright flash of light, afterimages are usually seen in negative. The photoisomerization is reversed by a series of enzymatic changes so that the retinal responds to more light energy.

Retinal Isomers



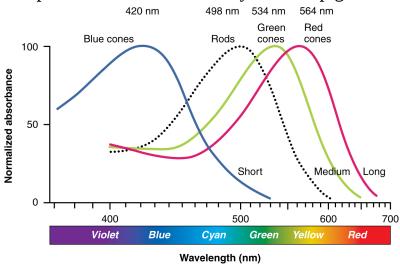
The retinal molecule has two isomers, (a) one before a photon interacts with it and (b) one that is altered through photoisomerization.

The opsins are sensitive to limited wavelengths of light. Rhodopsin, the photopigment in rods, is most sensitive to light at a wavelength of 498 nm. The three color opsins have peak sensitivities of 564 nm, 534 nm, and 420 nm corresponding roughly to the primary colors of red, green, and blue ([link]). The absorbance of rhodopsin in the rods is much more sensitive than in the cone opsins; specifically, rods are sensitive to vision in low light conditions, and cones are sensitive to brighter conditions. In normal sunlight, rhodopsin will be constantly bleached while the cones are active. In a darkened room, there is not enough light to activate cone opsins, and vision is entirely

dependent on rods. Rods are so sensitive to light that a single photon can result in an action potential from a rod's corresponding RGC.

The three types of cone opsins, being sensitive to different wavelengths of light, provide us with color vision. By comparing the activity of the three different cones, the brain can extract color information from visual stimuli. For example, a bright blue light that has a wavelength of approximately 450 nm would activate the "red" cones minimally, the "green" cones marginally, and the "blue" cones predominantly. The relative activation of the three different cones is calculated by the brain, which perceives the color as blue. However, cones cannot react to low-intensity light, and rods do not sense the color of light. Therefore, our low-light vision is—in essence—in grayscale. In other words, in a dark room, everything appears as a shade of gray. If you think that you can see colors in the dark, it is most likely because your brain knows what color something is and is relying on that memory.

Comparison of Color Sensitivity of Photopigments



Comparing the peak sensitivity and absorbance spectra of the four photopigments suggests that they are most sensitive to particular wavelengths.

Note:



Watch this <u>video</u> to learn more about a transverse section through the brain that depicts the visual pathway from the eye to the occipital cortex. The first half of the pathway is the projection from the RGCs through the optic nerve to the lateral geniculate nucleus in the thalamus on either side. This first fiber in the pathway synapses on a thalamic cell that then projects to the visual cortex in the occipital lobe where "seeing," or visual perception, takes place. This video gives an abbreviated overview of the visual system by concentrating on the pathway from the eyes to the occipital lobe. The video makes the statement (at 0:45) that "specialized cells in the retina called ganglion cells convert the light rays into electrical signals." What aspect of retinal processing is simplified by that statement? Explain your answer.

Sensory Nerves

Once any sensory cell transduces a stimulus into a nerve impulse, that impulse has to travel along axons to reach the CNS. In many of the special senses, the axons leaving the sensory receptors have a **topographical** arrangement, meaning that the location of the sensory receptor relates to the location of the axon in the nerve. For example, in the retina, axons from RGCs in the fovea are located at the center of the optic nerve, where they are surrounded by axons from the more peripheral RGCs.

Spinal Nerves

Generally, spinal nerves contain afferent axons from sensory receptors in the periphery, such as from the skin, mixed with efferent axons travelling to the muscles or other effector organs. As the spinal nerve nears the spinal cord, it splits into dorsal and ventral roots. The dorsal root contains only the axons of sensory neurons, whereas the ventral roots contain only the axons of the motor

neurons. Some of the branches will synapse with local neurons in the dorsal root ganglion, posterior (dorsal) horn, or even the anterior (ventral) horn, at the level of the spinal cord where they enter. Other branches will travel a short distance up or down the spine to interact with neurons at other levels of the spinal cord. A branch may also turn into the posterior (dorsal) column of the white matter to connect with the brain. For the sake of convenience, we will use the terms ventral and dorsal in reference to structures within the spinal cord that are part of these pathways. This will help to underscore the relationships between the different components. Typically, spinal nerve systems that connect to the brain are **contralateral**, in that the right side of the body is connected to the left side of the brain and the left side of the body to the right side of the brain.

Cranial Nerves

Cranial nerves convey specific sensory information from the head and neck directly to the brain. For sensations below the neck, the right side of the body is connected to the left side of the brain and the left side of the body to the right side of the brain. Whereas spinal information is contralateral, cranial nerve systems are mostly **ipsilateral**, meaning that a cranial nerve on the right side of the head is connected to the right side of the brain. Some cranial nerves contain only sensory axons, such as the olfactory, optic, and vestibulocochlear nerves. Other cranial nerves contain both sensory and motor axons, including the trigeminal, facial, glossopharyngeal, and vagus nerves (however, the vagus nerve is not associated with the somatic nervous system). The general senses of somatosensation for the face travel through the trigeminal system.

Chapter Review

The senses are olfaction (smell), gustation (taste), somatosensation (sensations associated with the skin and body), audition (hearing), equilibrium (balance), and vision. With the exception of somatosensation, this list represents the special senses, or those systems of the body that are associated with specific organs such as the tongue or eye. Somatosensation belongs to the general senses, which are those sensory structures that are distributed throughout the body and in the walls of various organs. The special senses are all primarily part of the somatic nervous system in that they are consciously perceived

through cerebral processes, though some special senses contribute to autonomic function. The general senses can be divided into somatosensation, which is commonly considered touch, but includes tactile, pressure, vibration, temperature, and pain perception. The general senses also include the visceral senses, which are separate from the somatic nervous system function in that they do not normally rise to the level of conscious perception.

The cells that transduce sensory stimuli into the electrochemical signals of the nervous system are classified on the basis of structural or functional aspects of the cells. The structural classifications are either based on the anatomy of the cell that is interacting with the stimulus (free nerve endings, encapsulated endings, or specialized receptor cell), or where the cell is located relative to the stimulus (interoceptor, exteroceptor, proprioceptor). Thirdly, the functional classification is based on how the cell transduces the stimulus into a neural signal. Chemoreceptors respond to chemical stimuli and are the basis for olfaction and gustation. Related to chemoreceptors are osmoreceptors and nociceptors for fluid balance and pain reception, respectively.

Mechanoreceptors respond to mechanical stimuli and are the basis for most aspects of somatosensation, as well as being the basis of audition and equilibrium in the inner ear. Thermoreceptors are sensitive to temperature changes, and photoreceptors are sensitive to light energy.

The nerves that convey sensory information from the periphery to the CNS are either spinal nerves, connected to the spinal cord, or cranial nerves, connected to the brain. Spinal nerves have mixed populations of fibers; some are motor fibers and some are sensory. The sensory fibers connect to the spinal cord through the dorsal root, which is attached to the dorsal root ganglion. Sensory information from the body that is conveyed through spinal nerves will project to the opposite side of the brain to be processed by the cerebral cortex. The cranial nerves can be strictly sensory fibers, such as the olfactory, optic, and vestibulocochlear nerves, or mixed sensory and motor nerves, such as the trigeminal, facial, glossopharyngeal, and vagus nerves. The cranial nerves are connected to the same side of the brain from which the sensory information originates.

Glossary

alkaloid

substance, usually from a plant source, that is chemically basic with respect to pH and will stimulate bitter receptors

amacrine cell

type of cell in the retina that connects to the bipolar cells near the outer synaptic layer and provides the basis for early image processing within the retina

ampulla

in the ear, the structure at the base of a semicircular canal that contains the hair cells and cupula for transduction of rotational movement of the head

anosmia

loss of the sense of smell; usually the result of physical disruption of the first cranial nerve

aqueous humor

watery fluid that fills the anterior chamber containing the cornea, iris, ciliary body, and lens of the eye

audition

sense of hearing

auricle

fleshy external structure of the ear

basilar membrane

in the ear, the floor of the cochlear duct on which the organ of Corti sits

bipolar cell

cell type in the retina that connects the photoreceptors to the RGCs

capsaicin

molecule that activates nociceptors by interacting with a temperaturesensitive ion channel and is the basis for "hot" sensations in spicy food

chemoreceptor

sensory receptor cell that is sensitive to chemical stimuli, such as in taste, smell, or pain

choroid

highly vascular tissue in the wall of the eye that supplies the outer retina with blood

ciliary body

smooth muscle structure on the interior surface of the iris that controls the shape of the lens through the zonule fibers

cochlea

auditory portion of the inner ear containing structures to transduce sound stimuli

cochlear duct

space within the auditory portion of the inner ear that contains the organ of Corti and is adjacent to the scala tympani and scala vestibuli on either side

cone photoreceptor

one of the two types of retinal receptor cell that is specialized for color vision through the use of three photopigments distributed through three separate populations of cells

conjunctiva

membrane attached to the inner surface of the eyelids that covers the anterior surface of the cornea

contralateral

word meaning "on the opposite side," as in axons that cross the midline in a fiber tract

cornea

fibrous covering of the anterior region of the eye that is transparent so that light can pass through it

cupula

specialized structure within the base of a semicircular canal that bends the stereocilia of hair cells when the head rotates by way of the relative movement of the enclosed fluid

encapsulated ending

configuration of a sensory receptor neuron with dendrites surrounded by specialized structures to aid in transduction of a particular type of sensation, such as the lamellated corpuscles in the deep dermis and subcutaneous tissue

equilibrium

sense of balance that includes sensations of position and movement of the head

external ear

structures on the lateral surface of the head, including the auricle and the ear canal back to the tympanic membrane

exteroceptor

sensory receptor that is positioned to interpret stimuli from the external environment, such as photoreceptors in the eye or somatosensory receptors in the skin

fovea

exact center of the retina at which visual stimuli are focused for maximal acuity, where the retina is thinnest, at which there is nothing but photoreceptors

free nerve ending

configuration of a sensory receptor neuron with dendrites in the connective tissue of the organ, such as in the dermis of the skin, that are most often sensitive to chemical, thermal, and mechanical stimuli

general sense

any sensory system that is distributed throughout the body and incorporated into organs of multiple other systems, such as the walls of the digestive organs or the skin

gustation

sense of taste

gustatory receptor cells

sensory cells in the taste bud that transduce the chemical stimuli of gustation

hair cells

mechanoreceptor cells found in the inner ear that transduce stimuli for the senses of hearing and balance

incus

(also, anvil) ossicle of the middle ear that connects the malleus to the stapes

inner ear

structure within the temporal bone that contains the sensory apparati of hearing and balance

inner segment

in the eye, the section of a photoreceptor that contains the nucleus and other major organelles for normal cellular functions

inner layer of the retina

layer in the retina where bipolar cells connect to RGCs

interoceptor

sensory receptor that is positioned to interpret stimuli from internal organs, such as stretch receptors in the wall of blood vessels

ipsilateral

word meaning on the same side, as in axons that do not cross the midline in a fiber tract

iris

colored portion of the anterior eye that surrounds the pupil

kinesthesia

sense of body movement based on sensations in skeletal muscles, tendons, joints, and the skin

kinocilium

largest sterecilia projecting from the receptor cell for equilibrium and audition

lacrimal duct

duct in the medial corner of the orbit that drains tears into the nasal cavity

lacrimal gland

gland lateral to the orbit that produces tears to wash across the surface of the eye

lens

component of the eye that focuses light on the retina

macula

enlargement at the base of a semicircular canal at which transduction of equilibrium stimuli takes place within the ampulla

malleus

(also, hammer) ossicle that is directly attached to the tympanic membrane

mechanoreceptor

receptor cell that transduces mechanical stimuli into an electrochemical signal

middle ear

space within the temporal bone between the ear canal and bony labyrinth where the ossicles amplify sound waves from the tympanic membrane to the oval window

neural tunic

layer of the eye that contains nervous tissue, namely the retina

nociceptor

receptor cell that senses pain stimuli

odorant molecules

volatile chemicals that bind to receptor proteins in olfactory neurons to stimulate the sense of smell

olfaction

sense of smell

olfactory bulb

central target of the first cranial nerve; located on the ventral surface of the frontal lobe in the cerebrum

olfactory epithelium

region of the nasal epithelium where olfactory neurons are located

olfactory receptor neuron

receptor cell of the olfactory system, sensitive to the chemical stimuli of smell, the axons of which compose the first cranial nerve

opsin

protein that contains the photosensitive cofactor retinal for phototransduction

optic disc

spot on the retina at which RGC axons leave the eye and blood vessels of the inner retina pass

optic nerve

second cranial nerve, which is responsible visual sensation

organ of Corti

structure in the cochlea in which hair cells transduce movements from sound waves into electrochemical signals

osmoreceptor

receptor cell that senses differences in the concentrations of bodily fluids on the basis of osmotic pressure

ossicles

three small bones in the middle ear

otolith

gelatinous substance in the utricle and saccule of the inner ear that contains calcium carbonate crystals and into which the stereocilia of hair cells are embedded

outer layer of the retina

layer in the retina at which photoreceptors connect to bipolar cells

outer segment

in the eye, the section of a photoreceptor that contains opsin molecules that transduce light stimuli

papilla

for gustation, a bump-like projection on the surface of the tongue that contains taste buds

photoisomerization

chemical change in the retinal molecule that alters the bonding so that it switches from the 11-*cis*-retinal isomer to the all-*trans*-retinal isomer

photon

individual "packet" of light

photoreceptor

receptor cell specialized to respond to light stimuli

proprioception

sense of position and movement of the body

proprioceptor

receptor cell that senses changes in the position and kinesthetic aspects of the body

pupil

open hole at the center of the iris that light passes through into the eye

receptor cell

cell that transduces environmental stimuli into neural signals

retina

nervous tissue of the eye at which phototransduction takes place

retinal

cofactor in an opsin molecule that undergoes a biochemical change when struck by a photon (pronounced with a stress on the last syllable)

retinal ganglion cell (RGC)

neuron of the retina that projects along the second cranial nerve

rhodopsin

photopigment molecule found in the rod photoreceptors

rod photoreceptor

one of the two types of retinal receptor cell that is specialized for low-light vision

round window

membrane that marks the end of the scala tympani

saccule

structure of the inner ear responsible for transducing linear acceleration in the vertical plane

scala tympani

portion of the cochlea that extends from the apex to the round window

scala vestibuli

portion of the cochlea that extends from the oval window to the apex

sclera

white of the eye

semicircular canals

structures within the inner ear responsible for transducing rotational movement information

sensory modality

a particular system for interpreting and perceiving environmental stimuli by the nervous system

somatosensation

general sense associated with modalities lumped together as touch

special sense

any sensory system associated with a specific organ structure, namely smell, taste, sight, hearing, and balance

stapes

(also, stirrup) ossicle of the middle ear that is attached to the inner ear

stereocilia

array of apical membrane extensions in a hair cell that transduce movements when they are bent

submodality

specific sense within a broader major sense such as sweet as a part of the sense of taste, or color as a part of vision

taste buds

structures within a papilla on the tongue that contain gustatory receptor cells

tectorial membrane

component of the organ of Corti that lays over the hair cells, into which the stereocilia are embedded

thermoreceptor

sensory receptor specialized for temperature stimuli

tip links

protein fibers that connect stereocilia to each other

topographical

relating to positional information

transduction

process of changing an environmental stimulus into the electrochemical signals of the nervous system

tympanic membrane

ear drum

umami

taste submodality for sensitivity to the concentration of amino acids; also called the savory sense

utricle

structure of the inner ear responsible for transducing linear acceleration in the horizontal plane

vestibular nerve

location of neuronal cell bodies that transmit equilibrium information along the eighth cranial nerve

vestibule

in the ear, the portion of the inner ear responsible for the sense of equilibrium

visceral sense

sense associated with the internal organs

vision

special sense of sight based on transduction of light stimuli

visual acuity

property of vision related to the sharpness of focus, which varies in relation to retinal position

vitreous humor

viscous fluid that fills the posterior chamber of the eye

zonular fibers

fibrous connections between the ciliary body and the lens

OU Human Physiology: Central Processing By the end of this section, you will be able to:

- Explain neural processing of visual input by the brain
- Describe the 'big picture" of the ascending sensory pathways from the sensory stimulus to the spinal cord to the medulla, midbrain, and the thalamus using the terms first-order, second-order, and third-order neurons to the appropriate area of the cerebral cortex based on whether the sensory information is somatosensory, gustatory, auditory, equilibrium, or vision
- Explain the importance of the thalamus in processing sensory information
- Explain the role of the ventral horn of the spinal cord

Sensory Pathways

Specific regions of the CNS coordinate different somatic processes using sensory inputs and motor outputs of peripheral nerves. A simple case is a reflex caused by a synapse between a dorsal sensory neuron axon and a motor neuron in the ventral horn. More complex arrangements are possible to integrate peripheral sensory information with higher processes. The important regions of the CNS that play a role in somatic processes can be separated into the spinal cord brain stem, diencephalon, cerebral cortex, and subcortical structures.

Spinal Cord and Brain Stem

A sensory pathway that carries peripheral sensations to the brain is referred to as an **ascending pathway**, or ascending tract. The various sensory modalities each follow specific pathways through the CNS. Tactile and other somatosensory stimuli activate receptors in the skin, muscles, tendons, and joints throughout the entire body. However, the somatosensory pathways are divided into two separate systems on the basis of the location of the receptor neurons. Somatosensory stimuli from below the neck pass along the sensory pathways of the spinal cord, whereas somatosensory

stimuli from the head and neck travel through the cranial nerves—specifically, the trigeminal system.

The **dorsal column system** (sometimes referred to as the dorsal column—medial lemniscus) and the **spinothalamic tract** are two major pathways that bring sensory information to the brain ([link]). The sensory pathways in each of these systems are composed of three successive neurons; s first order, second order, and third order neuron.

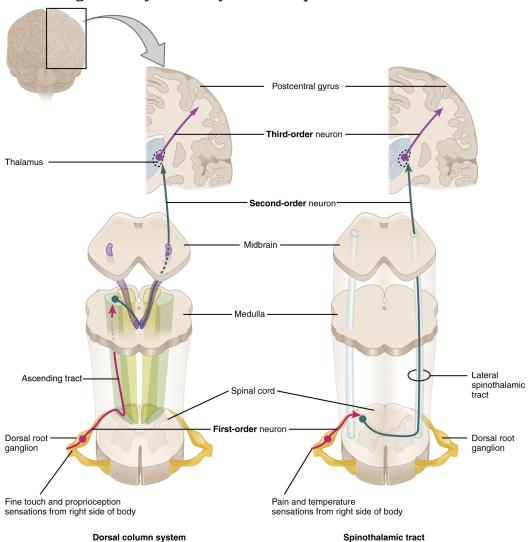
The dorsal column system begins with the axon of a dorsal root ganglion neuron (the first order neuron) entering the dorsal root and joining the dorsal column white matter in the spinal cord. The axons in the dorsal column terminate in the nuclei of the medulla, and synapse with a second neuron (the second order neuron). This second neuron projects from one of the two nuclei and then **decussates**, or crosses the midline of the medulla. These axons then continue to ascend the brain stem as a bundle. These axons terminate in the thalamus, where each synapses with a third neuron (the third order neuron). The third order neuron projects its axons to the postcentral gyrus of the cerebral cortex, where somatosensory stimuli are initially processed and the conscious perception of the stimulus occurs.

The spinothalamic tract also begins with neurons in a dorsal root ganglion (the first order neuron). These neurons extend their axons to the dorsal horn, where they synapse with the second neuron (the second order neuron). The name "spinothalamic" comes from this second neuron, which has its cell body in the spinal cord gray matter and connects to the thalamus. Axons from these second order neurons then decussate (cross the midline) within the spinal cord and ascend to the brain and enter the thalamus, where each synapses with the third neuron (the third order neuron). The third order neurons in the thalamus project their axons to the spinothalamic tract, which synapses in the postcentral gyrus of the cerebral cortex.

These two systems (the dorsal column system and the spinothalamic tract) are similar in that they both begin with dorsal root ganglion cells, as with most general sensory information. The dorsal column system is primarily responsible for touch sensations and proprioception, whereas the spinothalamic tract pathway is primarily responsible for pain and temperature sensations. Another similarity is that the second order neurons

in both of these pathways are contralateral, because they project across the midline to the other side of the brain or spinal cord. In the dorsal column system, this decussation takes place in the brain stem; in the spinothalamic pathway, it takes place in the spinal cord at the same spinal cord level at which the information entered. The third order neurons in the two pathways are essentially the same. In both, the second order neuron synapses in the thalamus, and the third order neuron projects to the somatosensory cortex.

Ascending Sensory Pathways of the Spinal Cord



The dorsal column system and spinothalamic tract are the major ascending pathways that connect the periphery with the brain.

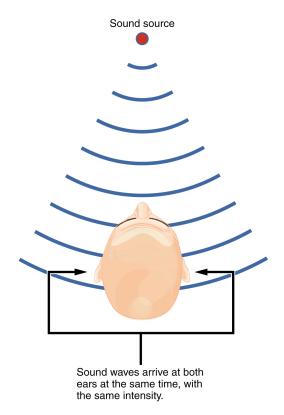
The trigeminal pathway carries somatosensory information from the face, head, mouth, and nasal cavity. As with the previously discussed nerve tracts, the sensory pathways of the trigeminal pathway each involve three successive neurons. Axons from the third neuron project from the thalamus to the primary somatosensory cortex of the cerebrum.

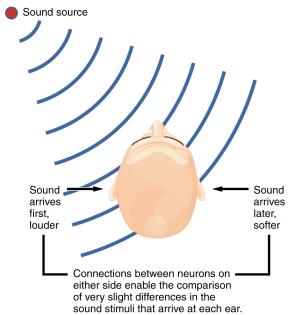
The sensory pathway for gustation travels along the facial and glossopharyngeal cranial nerves, which synapse with neurons in the brain stem, which project to the thalamus and synapse with neurons that project to the gustatory cortex of the cerebral cortex, where taste is processed and consciously perceived.

The sensory pathway for hearing travels along the vestibulocochlear nerve, which synapses with neurons in the medulla. Within the brain stem, input from either ear is combined to extract location information from the auditory stimuli. Whereas the initial auditory stimuli received at the cochlea strictly represent the frequency—or pitch—of the stimuli, the locations of sounds can be determined by comparing information arriving at both ears.

Sound localization is a feature of central processing in the brain stem. Sound localization is achieved by the brain calculating the **interaural time difference** and the **interaural intensity difference**. A sound originating from a specific location will arrive at each ear at different times, unless the sound is directly in front of the listener. If the sound source is slightly to the left of the listener, the sound will arrive at the left ear microseconds before it arrives at the right ear ([link]). This time difference is an example of an interaural time difference. Also, the sound will be slightly louder in the left ear than in the right ear because some of the sound waves reaching the opposite ear are blocked by the head. This is an example of an interaural intensity difference.

Auditory Brain Stem Mechanisms of Sound Localization





Localizing sound in the horizontal plane is achieved by processing in the medullary nuclei of the auditory system. Connections between neurons

on either side are able to compare very slight differences in sound stimuli that arrive at either ear and represent interaural time and intensity differences.

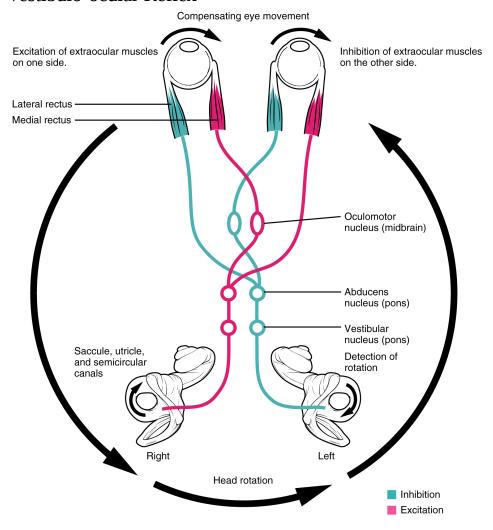
Auditory processing continues on to the midbrain called the inferior colliculus. Axons from the inferior colliculus project to two locations, the thalamus and the superior colliculus. The medial geniculate nucleus of the thalamus receives the auditory information and then projects that information to the auditory cortex in the temporal lobe of the cerebral cortex. The superior colliculus receives input from the visual and somatosensory systems, as well as the ears, to initiate stimulation of the muscles that turn the head and neck toward the auditory stimulus.

Balance is coordinated through the vestibular system, the nerves of which are composed of axons from the vestibular ganglion that carries information from the utricle, saccule, and semicircular canals. The system contributes to controlling head and neck movements in response to vestibular signals. An important function of the vestibular system is coordinating eye and head movements to maintain visual attention. Most of the axons terminate in the vestibular nuclei of the medulla. Some axons project from the vestibular ganglion directly to the cerebellum, with no intervening synapse in the vestibular nuclei. The cerebellum is primarily responsible for initiating movements on the basis of equilibrium information.

Neurons in the vestibular nuclei project their axons to targets in the brain stem. One target is the reticular formation, which influences respiratory and cardiovascular functions in relation to body movements. A second target of the axons of neurons in the vestibular nuclei is the spinal cord, which initiates the spinal reflexes involved with posture and balance. To assist the visual system, fibers of the vestibular nuclei project to the oculomotor, trochlear, and abducens nuclei to influence signals sent along the cranial nerves. These connections constitute the pathway of the **vestibulo-ocular**

reflex (VOR), which compensates for head and body movement by stabilizing images on the retina ([link]). Finally, the vestibular nuclei project to the thalamus to join the proprioceptive pathway of the dorsal column system, allowing conscious perception of equilibrium.

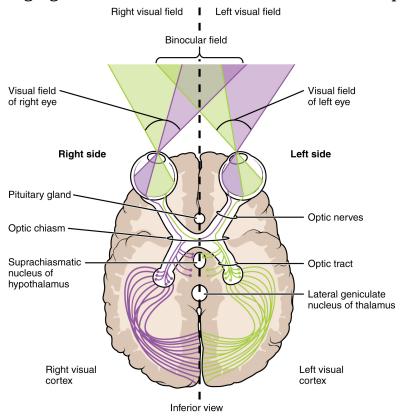
Vestibulo-ocular Reflex



Connections between the vestibular system and the cranial nerves controlling eye movement keep the eyes centered on a visual stimulus, even though the head is moving. During head movement, the eye muscles move the eyes in the opposite direction as the head movement, keeping the visual stimulus centered in the field of view.

The connections of the optic nerve are more complicated than those of other cranial nerves. Instead of the connections being between each eye and the brain, visual information is segregated between the left and right sides of the visual field. In addition, some of the information from one side of the visual field projects to the opposite side of the brain. Within each eye, the axons projecting from the medial side of the retina decussate at the **optic chiasm**. For example, the axons from the medial retina of the left eye cross over to the right side of the brain at the optic chiasm. However, within each eye, the axons projecting from the lateral side of the retina do not decussate. For example, the axons from the lateral retina of the right eye project back to the right side of the brain. Therefore the left field of view of each eye is processed on the right side of the brain, whereas the right field of view of each eye is processed on the left side of the brain ([link]).

Segregation of Visual Field Information at the Optic Chiasm



Contralateral visual field information from the lateral retina projects to the ipsilateral brain, whereas ipsilateral visual field information has to decussate at the optic chiasm to reach the opposite side of the brain.

A unique clinical presentation that relates to this anatomic arrangement is the loss of lateral peripheral vision, known as bilateral hemianopia. This is different from "tunnel vision" because the superior and inferior peripheral fields are not lost. Visual field deficits can be disturbing for a patient, but in this case, the cause is not within the visual system itself. A growth of the pituitary gland presses against the optic chiasm and interferes with signal transmission. However, the axons projecting to the same side of the brain are unaffected. Therefore, the patient loses the outermost areas of their field of vision and cannot see objects to their right and left.

Extending from the optic chiasm, the axons of the visual system are referred to as the **optic tract** instead of the optic nerve. The optic tract has three major targets, two in the diencephalon and one in the midbrain. The connection between the eyes and diencephalon is demonstrated during development, in which the neural tissue of the retina differentiates from that of the diencephalon by the growth of the secondary vesicles. The connections of the retina into the CNS are a holdover from this developmental association. The majority of the connections of the optic tract are to the thalamus—specifically, the **lateral geniculate nucleus**. Axons from this nucleus then project to the visual cortex of the cerebrum, located in the occipital lobe. Another target of the optic tract is the superior colliculus.

In addition, a very small number of RGC axons project from the optic chiasm to the **suprachiasmatic nucleus** of the hypothalamus. These RGCs are photosensitive, in that they respond to the presence or absence of light. Unlike the photoreceptors, however, these photosensitive RGCs cannot be used to perceive images. By simply responding to the absence or presence of light, these RGCs can send information about day length. The perceived proportion of sunlight to darkness establishes the **circadian rhythm** of our

bodies, allowing certain physiological events to occur at approximately the same time every day.

Diencephalon

The diencephalon is beneath the cerebrum and includes the thalamus and hypothalamus. In the somatic nervous system, the thalamus is an important relay for communication between the cerebrum and the rest of the nervous system. The hypothalamus has both somatic and autonomic functions. In addition, the hypothalamus communicates with the limbic system, which controls emotions and memory functions.

Sensory input to the thalamus comes from most of the special senses and ascending somatosensory tracts. Each sensory system is relayed through a particular nucleus in the thalamus. The thalamus is a required transfer point for most sensory tracts that reach the cerebral cortex, where conscious sensory perception begins. The one exception to this rule is the olfactory system. The olfactory tract axons from the olfactory bulb project directly to the cerebral cortex, along with the limbic system and hypothalamus.

The thalamus is a collection of several nuclei that can be categorized into three anatomical groups. White matter running through the thalamus defines the three major regions of the thalamus, which are an anterior nucleus, a medial nucleus, and a lateral group of nuclei. The anterior nucleus serves as a relay between the hypothalamus and the emotion and memory-producing limbic system. The medial nuclei serve as a relay for information from the limbic system and basal ganglia to the cerebral cortex. This allows memory creation during learning, but also determines alertness. The special and somatic senses connect to the lateral nuclei, where their information is relayed to the appropriate sensory cortex of the cerebrum.

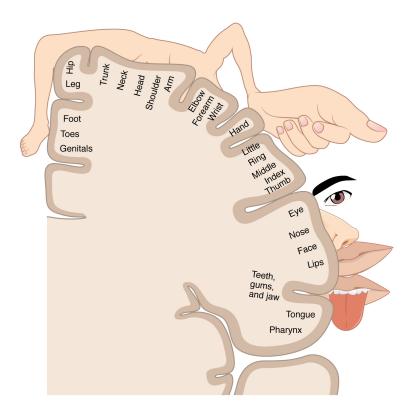
Cortical Processing

As described earlier, many of the sensory axons are positioned in the same way as their corresponding receptor cells in the body. This allows identification of the position of a stimulus on the basis of which receptor

cells are sending information. The cerebral cortex also maintains this sensory topography in the particular areas of the cortex that correspond to the position of the receptor cells. The somatosensory cortex provides an example in which, in essence, the locations of the somatosensory receptors in the body are mapped onto the somatosensory cortex. This mapping is often depicted using a **sensory homunculus** ([link]).

The term homunculus comes from the Latin word for "little man" and refers to a map of the human body that is laid across a portion of the cerebral cortex. In the somatosensory cortex, the external genitals, feet, and lower legs are represented on the medial face of the gyrus within the longitudinal fissure. As the gyrus curves out of the fissure and along the surface of the parietal lobe, the body map continues through the thighs, hips, trunk, shoulders, arms, and hands. The head and face are just lateral to the fingers as the gyrus approaches the lateral sulcus. The representation of the body in this topographical map is medial to lateral from the lower to upper body. It is a continuation of the topographical arrangement seen in the dorsal column system. Also, the head and neck axons running from the trigeminal nuclei to the thalamus run adjacent to the upper body fibers. The connections through the thalamus maintain topography such that the anatomic information is preserved. Note that this correspondence does not result in a perfectly miniature scale version of the body, but rather exaggerates the more sensitive areas of the body, such as the fingers and lower face. Less sensitive areas of the body, such as the shoulders and back, are mapped to smaller areas on the cortex.

The Sensory Homunculus



A cartoon representation of the sensory homunculus arranged adjacent to the cortical region in which the processing takes place.

Note:



Go watch this video to learn more about the sensory homunculus.

Likewise, the topographic relationship between the retina and the visual cortex is maintained throughout the visual pathway. The visual field is projected onto the two retinae, as described above, with sorting at the optic chiasm. The right peripheral visual field falls on the medial portion of the right retina and the lateral portion of the left retina. The right medial retina then projects across the midline through the optic chiasm. This results in the right visual field being processed in the left visual cortex. Likewise, the left visual field is processed in the right visual cortex (see [link]). Though the chiasm is helping to sort right and left visual information, superior and inferior visual information is maintained topographically in the visual pathway. Light from the superior visual field falls on the inferior retina, and light from the inferior visual field falls on the superior retina. This topography is maintained such that the superior region of the visual cortex processes the inferior visual field and vice versa. Therefore, the visual field information is inverted and reversed as it enters the visual cortex—up is down, and left is right. However, the cortex processes the visual information such that the final conscious perception of the visual field is correct. The topographic relationship is evident in that information from the foveal region of the retina is processed in the center of the primary visual cortex. Information from the peripheral regions of the retina are correspondingly processed toward the edges of the visual cortex. Similar to the exaggerations in the sensory homunculus of the somatosensory cortex, the foveal-processing area of the visual cortex is disproportionately larger than the areas processing peripheral vision.

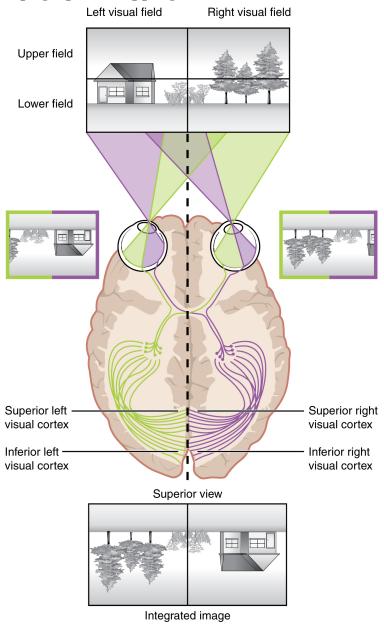
Note:



Go watch this <u>video</u> to learn more about visual processing.

In an experiment performed in the 1960s, subjects wore prism glasses so that the visual field was inverted before reaching the eye. On the first day of the experiment, subjects would duck when walking up to a table, thinking it was suspended from the ceiling. However, after a few days of acclimation, the subjects behaved as if everything were represented correctly. Therefore, the visual cortex is somewhat flexible in adapting to the information it receives from our eyes ([link]).

Topographic Mapping of the Retina onto the Visual Cortex



The visual field projects onto the retina

through the lenses and falls on the retinae as an inverted, reversed image. The topography of this image is maintained as the visual information travels through the visual pathway to the cortex.

The cortex has been described as having specific regions that are responsible for processing specific information; there is the visual cortex, somatosensory cortex, gustatory cortex, etc. However, our experience of these senses is not divided. Instead, we experience what can be referred to as a seamless percept. Our perceptions of the various sensory modalities—though distinct in their content—are integrated by the brain so that we experience the world as a continuous whole.

In the cerebral cortex, sensory processing begins at the **primary sensory cortex**, then proceeds to an **association area**, and finally, into a multimodal integration area. For example, the visual pathway projects from the retinae through the thalamus to the primary visual cortex in the occipital lobe. Here, visual stimuli begin to be recognized as basic shapes. Edges of objects are recognized and built into more complex shapes. Also, inputs from both eyes are compared to extract depth information. Because of the overlapping field of view between the two eyes, the brain can begin to estimate the distance of stimuli based on binocular depth cues.

Note:



Watch this <u>video</u> to learn more about how the brain perceives 3-D motion. Similar to how retinal disparity offers 3-D moviegoers a way to extract 3-D information from the two-dimensional visual field projected onto the retina, the brain can extract information about movement in space by comparing what the two eyes see. If movement of a visual stimulus is leftward in one eye and rightward in the opposite eye, the brain interprets this as movement toward (or away) from the face along the midline. If both eyes see an object moving in the same direction, but at different rates, what would that mean for spatial movement?

Note:

Everyday Connections

Depth Perception, 3-D Movies, and Optical Illusions

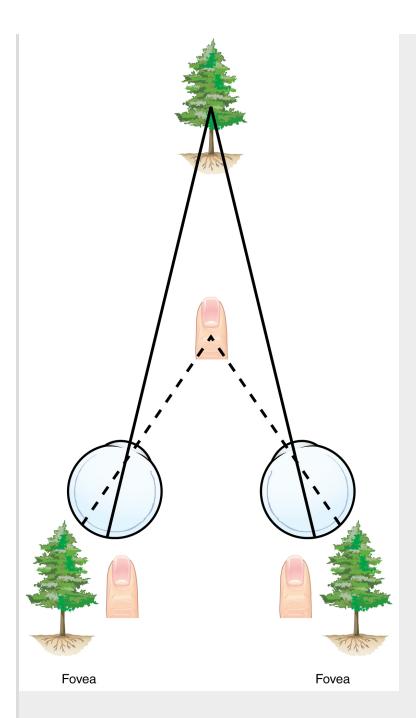
The visual field is projected onto the retinal surface, where photoreceptors transduce light energy into neural signals for the brain to interpret. The retina is a two-dimensional surface, so it does not encode three-dimensional information. However, we can perceive depth. How is that accomplished?

Two ways in which we can extract depth information from the two-dimensional retinal signal are based on monocular cues and binocular cues, respectively. Monocular depth cues are those that are the result of information within the two-dimensional visual field. One object that overlaps another object has to be in front. Relative size differences are also a cue. For example, if a basketball appears larger than the basket, then the basket must be further away. On the basis of experience, we can estimate how far away the basket is. Binocular depth cues compare information represented in the two retinae because they do not see the visual field exactly the same.

The centers of the two eyes are separated by a small distance, which is approximately 6 to 6.5 cm in most people. Because of this offset, visual stimuli do not fall on exactly the same spot on both retinae unless we are fixated directly on them and they fall on the fovea of each retina. All other objects in the visual field, either closer or farther away than the fixated object, will fall on different spots on the retina. When vision is fixed on an object in space, closer objects will fall on the lateral retina of each eye, and

more distant objects will fall on the medial retina of either eye ([link]). This is easily observed by holding a finger up in front of your face as you look at a more distant object. You will see two images of your finger that represent the two disparate images that are falling on either retina. These depth cues, both monocular and binocular, can be exploited to make the brain think there are three dimensions in two-dimensional information. This is the basis of 3-D movies. The projected image on the screen is two dimensional, but it has disparate information embedded in it. The 3-D glasses that are available at the theater filter the information so that only one eye sees one version of what is on the screen, and the other eye sees the other version. If you take the glasses off, the image on the screen will have varying amounts of blur because both eyes are seeing both layers of information, and the third dimension will not be evident. Some optical illusions can take advantage of depth cues as well, though those are more often using monocular cues to fool the brain into seeing different parts of the scene as being at different depths.

Retinal Disparity



Because of the interocular distance, which results in objects of different distances falling on different spots of the two retinae, the brain can extract depth perception from the two-dimensional information of the visual field.

Note:

Disorders of the...

Brain: Prosopagnosia

The failures of sensory perception can be unusual and debilitating. A particular sensory deficit that inhibits an important social function of humans is prosopagnosia, or face blindness. The word comes from the Greek words prosopa, that means "faces," and agnosia, that means "not knowing." Some people may feel that they cannot recognize people easily by their faces. However, a person with prosopagnosia cannot recognize the most recognizable people in their respective cultures. They would not recognize the face of a celebrity, an important historical figure, or even a family member like their mother. They may not even recognize their own face.

Prosopagnosia can be caused by trauma to the brain, or it can be present from birth. The exact cause of proposagnosia and the reason that it happens to some people is unclear. A study of the brains of people born with the deficit found that a specific region of the brain, the anterior fusiform gyrus of the temporal lobe, is often underdeveloped. This region of the brain is concerned with the recognition of visual stimuli and its possible association with memories. Though the evidence is not yet definitive, this region is likely to be where facial recognition occurs.

Though this can be a devastating condition, people who suffer from it can get by—often by using other cues to recognize the people they see. Often, the sound of a person's voice, or the presence of unique cues such as distinct facial features (a mole, for example) or hair color can help the sufferer recognize a familiar person. In the video on prosopagnosia provided in this section, a woman is shown having trouble recognizing celebrities, family members, and herself. In some situations, she can use other cues to help her recognize faces.

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The inability to recognize people by their faces is a troublesome problem. It can be caused by trauma, or it may be inborn. Watch this <u>video</u> to learn more about a person who lost the ability to recognize faces as the result of an injury. She cannot recognize the faces of close family members or herself. What other information can a person suffering from prosopagnosia use to figure out whom they are seeing?

Chapter Review

Sensory input to the brain enters through pathways that travel through either the spinal cord (for somatosensory input from the body) or the brain stem (for everything else, except the visual and olfactory systems) to reach the diencephalon. In the diencephalon, sensory pathways reach the thalamus. This is necessary for all sensory systems to reach the cerebral cortex, except for the olfactory system that is directly connected to the frontal and temporal lobes.

The two major tracts in the spinal cord, originating from sensory neurons in the dorsal root ganglia, are the dorsal column system and the spinothalamic tract. The major differences between the two are in the type of information that is relayed to the brain and where the tracts decussate. The dorsal column system primarily carries information about touch and proprioception and crosses the midline in the medulla. The spinothalamic tract is primarily responsible for pain and temperature sensation and crosses the midline in the spinal cord at the level at which it enters. The trigeminal nerve adds similar sensation information from the head to these pathways.

The auditory pathway passes through multiple nuclei in the brain stem in which additional information is extracted from the basic frequency stimuli

processed by the cochlea. Sound localization is made possible through the activity of these brain stem structures. The vestibular system enters the brain stem and influences activity in the cerebellum, spinal cord, and cerebral cortex.

The visual pathway segregates information from the two eyes so that one half of the visual field projects to the other side of the brain. Within visual cortical areas, the perception of the stimuli and their location is passed along two streams, one ventral and one dorsal. The ventral visual stream connects to structures in the temporal lobe that are important for long-term memory formation. The dorsal visual stream interacts with the somatosensory cortex in the parietal lobe, and together they can influence the activity in the frontal lobe to generate movements of the body in relation to visual information.

Glossary

ascending pathway

fiber structure that relays sensory information from the periphery through the spinal cord and brain stem to other structures of the brain

association area

region of cortex connected to a primary sensory cortical area that further processes the information to generate more complex sensory perceptions

circadian rhythm

internal perception of the daily cycle of light and dark based on retinal activity related to sunlight

decussate

to cross the midline, as in fibers that project from one side of the body to the other

dorsal column system

ascending tract of the spinal cord associated with fine touch and proprioceptive sensations

lateral geniculate nucleus

thalamic target of the RGCs that projects to the visual cortex

optic chiasm

decussation point in the visual system at which medial retina fibers cross to the other side of the brain

optic tract

name for the fiber structure containing axons from the retina posterior to the optic chiasm representing their CNS location

primary sensory cortex

region of the cerebral cortex that initially receives sensory input from an ascending pathway from the thalamus and begins the processing that will result in conscious perception of that modality

sensory homunculus

topographic representation of the body within the somatosensory cortex demonstrating the correspondence between neurons processing stimuli and sensitivity

spinothalamic tract

ascending tract of the spinal cord associated with pain and temperature sensations

suprachiasmatic nucleus

hypothalamic target of the retina that helps to establish the circadian rhythm of the body on the basis of the presence or absence of daylight

vestibulo-ocular reflex (VOR)

reflex based on connections between the vestibular system and the cranial nerves of eye movements that ensures images are stabilized on the retina as the head and body move

OU Human Physiology: Motor Responses By the end of this section, you will be able to:

- Explain neural processing of visual input by the brain
- Describe the 'big picture" of the ascending sensory pathways from the sensory stimulus to the spinal cord to the medulla, midbrain, and the thalamus using the terms first-order, second-order, and third-order neurons to the appropriate area of the cerebral cortex based on whether the sensory information is somatosensory, gustatory, auditory, equilibrium, or vision
- Explain the importance of the thalamus in processing sensory information
- Explain the role of the ventral horn of the spinal cord

The defining characteristic of the somatic nervous system is that it controls skeletal muscles. Somatic senses inform the nervous system about the external environment, but the response to that is through voluntary muscle movement. The term "voluntary" suggests that there is a conscious decision to make a movement. However, some aspects of the somatic system use voluntary muscles without conscious control. One example is the ability of our breathing to switch to unconscious control while we are focused on another task. However, the muscles that are responsible for the basic process of breathing are also utilized for speech, which is entirely voluntary.

Cortical Responses

Let's start with sensory stimuli that have been registered through receptor cells and the information relayed to the CNS along ascending pathways. In the cerebral cortex, the initial processing of sensory perception progresses to associative processing and then integration in multimodal areas of cortex. These levels of processing can lead to the incorporation of sensory perceptions into memory, but more importantly, they lead to a response. The completion of cortical processing through the primary, associative, and integrative sensory areas initiates a similar progression of motor processing, usually in different cortical areas.

Whereas the sensory cortical areas are located in the occipital, temporal, and parietal lobes, motor functions are largely controlled by the frontal lobe. The most anterior regions of the frontal lobe—the prefrontal areas—are important for executive functions, which are those cognitive functions that lead to goal-directed behaviors. These higher cognitive processes include working memory, which has been called a "mental scratch pad," that can help organize and represent information that is not in the immediate environment. The prefrontal lobe is responsible for aspects of attention, such as inhibiting distracting thoughts and actions so that a person can focus on a goal and direct behavior toward achieving that goal.

The functions of the prefrontal cortex are integral to the personality of an individual, because it is largely responsible for what a person intends to do and how they accomplish those plans. A famous case of damage to the prefrontal cortex is that of Phineas Gage, dating back to 1848. He was a railroad worker who had a metal spike impale his prefrontal cortex ([link]). He survived the accident, but according to second-hand accounts, his personality changed drastically. Friends described him as no longer acting like himself. Whereas he was a hardworking, amiable man before the accident, he turned into an irritable, temperamental, and lazy man after the accident. Many of the accounts of his change may have been inflated in the retelling, and some behavior was likely attributable to alcohol used as a pain medication. However, the accounts suggest that some aspects of his personality did change. Also, there is new evidence that though his life changed dramatically, he was able to become a functioning stagecoach driver, suggesting that the brain has the ability to recover even from major trauma such as this.

Phineas Gage





The victim of an accident while working on a railroad in 1848, Phineas Gage had a large iron rod impaled through the prefrontal cortex of his frontal lobe. After the accident, his personality appeared to change, but he eventually learned to cope with the trauma and lived as a coach driver even after such a traumatic event. (credit b: John M. Harlow, MD)

Descending Pathways

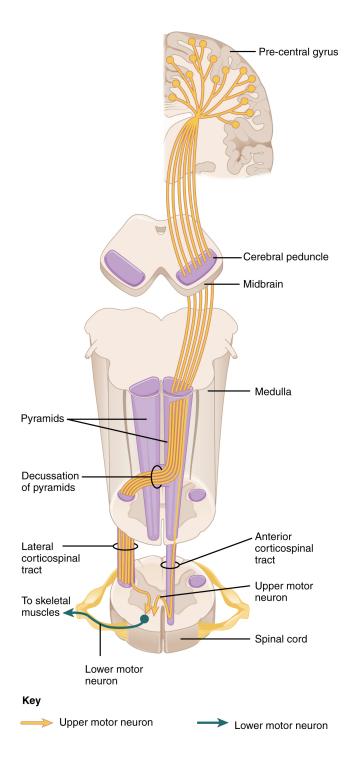
The motor output from the cortex descends into the brain stem and to the spinal cord to control the musculature through motor neurons. Neurons located in the primary motor cortex synapse with lower motor neurons in

the spinal cord or the brain stem. The two descending pathways travelle;d by the axons are the corticospinal tract and the corticobulbar tract. Both tracts are named for their origin in the cortex and their targets—either the spinal cord or the brain stem (the term "bulbar" refers to the brain stem as the bulb, or enlargement, at the top of the spinal cord).

These two descending pathways are responsible for the conscious or voluntary movements of skeletal muscles. Any motor command from the primary motor cortex is sent down the axons to activate upper motor neurons in either the cranial motor nuclei or in the ventral horn of the spinal cord. The axons of the corticobulbar tract are ipsilateral, meaning they project from the cortex to the motor nucleus on the same side of the nervous system. Conversely, the axons of the corticospinal tract are largely contralateral, meaning that they cross the midline of the brain stem or spinal cord and synapse on the opposite side of the body. Therefore, the right motor cortex of the cerebrum controls muscles on the left side of the body, and vice versa.

The corticospinal tract descends from the cortex through the deep white matter of the cerebrum. It then passes between the caudate nucleus and putamen of the basal nuclei as a bundle. The tract then passes through the midbrain, after which it burrows through the pons. Upon entering the medulla, the tracts make up the large white matter tract referred to as the **pyramids** ([link]). The defining landmark of the medullary-spinal border is the **pyramidal decussation**, which is where most of the fibers in the corticospinal tract cross over to the opposite side of the brain. At this point, the tract separates into two parts, which have control over different domains of the musculature.

Corticospinal Tract



The major descending tract that controls skeletal muscle movements is the corticospinal tract. It is composed of two neurons, the upper motor neuron

and the lower motor neuron. The upper motor neuron has its cell body in the primary motor cortex of the frontal lobe and synapses on the lower motor neuron, which is in the ventral horn of the spinal cord and projects to the skeletal muscle in the periphery.

Appendicular Control

The lateral corticospinal tract is composed of the fibers that cross the midline at the pyramidal decussation (see [link]). The axons cross over from the anterior position of the pyramids in the medulla to the lateral column of the spinal cord. These axons are responsible for controlling appendicular muscles.

Axial Control

The anterior corticospinal tract is responsible for controlling the muscles of the body trunk (see [link]). These axons do not decussate in the medulla. Instead, they remain in an anterior position as they descend the brain stem and enter the spinal cord. These axons then travel to the spinal cord level at which they synapse with a lower motor neuron. Upon reaching the appropriate level, the axons decussate, entering the ventral horn on the opposite side of the spinal cord from which they entered. In the ventral horn, these axons synapse with their corresponding lower motor neurons. The lower motor neurons are located in the medial regions of the ventral horn, because they control the axial muscles of the trunk.

Because movements of the body trunk involve both sides of the body, the anterior corticospinal tract is not entirely contralateral. Some collateral

branches of the tract will project into the ipsilateral ventral horn to control synergistic muscles on that side of the body, or to inhibit antagonistic muscles through interneurons within the ventral horn. Through the influence of both sides of the body, the anterior corticospinal tract can coordinate postural muscles in broad movements of the body. These coordinating axons in the anterior corticospinal tract are often considered bilateral, as they are both ipsilateral and contralateral.

Note:



Watch this <u>video</u> to learn more about the descending motor pathway for the somatic nervous system. The autonomic connections are mentioned, which are covered in another chapter. From this brief video, only some of the descending motor pathway of the somatic nervous system is described. Which division of the pathway is described and which division is left out?

Extrapyramidal Controls

Other descending connections between the brain and the spinal cord are called the extrapyramidal system. The name comes from the fact that this system is outside the corticospinal pathway, which includes the pyramids in the medulla. A few pathways originating from the brain stem contribute to this system.

The tectospinal tract projects from the midbrain to the spinal cord and is important for postural movements. The reticulospinal tract connects the reticular system, a diffuse region of gray matter in the brain stem, with the spinal cord. This tract influences trunk and proximal limb muscles related

to posture and locomotion. The reticulospinal tract also contributes to muscle tone and influences autonomic functions. The vestibulospinal tract connects the brain stem nuclei of the vestibular system with the spinal cord. This allows posture, movement, and balance to be modulated on the basis of equilibrium information provided by the vestibular system.

The pathways of the extrapyramidal system are influenced by subcortical structures. For example, connections between the secondary motor cortices and the extrapyramidal system modulate spine and cranium movements. The basal nuclei, which are important for regulating movement initiated by the CNS, influence the extrapyramidal system as well as its thalamic feedback to the motor cortex.

The conscious movement of our muscles is more complicated than simply sending a single command from the precentral gyrus down to the proper motor neurons. During the movement of any body part, our muscles relay information back to the brain, and the brain is constantly sending "revised" instructions back to the muscles. The cerebellum is important in contributing to the motor system because it compares cerebral motor commands with proprioceptive feedback. The corticospinal fibers that project to the ventral horn of the spinal cord have branches that also synapse in the pons, which project to the cerebellum. Also, the proprioceptive sensations of the dorsal column system have a collateral projection to the medulla that projects to the cerebellum. These two streams of information are compared in the cerebellar cortex. Conflicts between the motor commands sent by the cerebrum and body position information provided by the proprioceptors cause the cerebellum to stimulate the red nucleus of the midbrain. The red nucleus then sends corrective commands to the spinal cord along the rubrospinal tract. The name of this tract comes from the word for red that is seen in the English word "ruby."

A good example of how the cerebellum corrects cerebral motor commands can be illustrated by walking in water. An original motor command from the cerebrum to walk will result in a highly coordinated set of learned movements. However, in water, the body cannot actually perform a typical walking movement as instructed. The cerebellum can alter the motor command, stimulating the leg muscles to take larger steps to overcome the

water resistance. The cerebellum can make the necessary changes through the rubrospinal tract. Modulating the basic command to walk also relies on spinal reflexes, but the cerebellum is responsible for calculating the appropriate response. When the cerebellum does not work properly, coordination and balance are severely affected. The most dramatic example of this is during the overconsumption of alcohol. Alcohol inhibits the ability of the cerebellum to interpret proprioceptive feedback, making it more difficult to coordinate body movements, such as walking a straight line, or guide the movement of the hand to touch the tip of the nose.

Note:



Visit this <u>site</u> to read about an elderly woman who starts to lose the ability to control fine movements, such as speech and the movement of limbs. Many of the usual causes were ruled out. It was not a stroke, Parkinson's disease, diabetes, or thyroid dysfunction. The next most obvious cause was medication, so her pharmacist had to be consulted. The side effect of a drug meant to help her sleep had resulted in changes in motor control. What regions of the nervous system are likely to be the focus of haloperidol side effects?

Ventral Horn Output

The somatic nervous system provides output strictly to skeletal muscles. The lower motor neurons, which are responsible for the contraction of these muscles, are found in the ventral horn of the spinal cord. These large, multipolar neurons have a corona of dendrites surrounding the cell body and an axon that extends out of the ventral horn. This axon travels through

the ventral nerve root to join the emerging spinal nerve. The axon is relatively long because it needs to reach muscles in the periphery of the body. The diameters of cell bodies may be on the order of hundreds of micrometers to support the long axon; some axons are a meter in length, such as the lumbar motor neurons that innervate muscles in the first digits of the feet.

The axons will also branch to innervate multiple muscle fibers. Together, the motor neuron and all the muscle fibers that it controls make up a motor unit. Motor units vary in size. Some may contain up to 1000 muscle fibers, such as in the quadriceps, or they may only have 10 fibers, such as in an extraocular muscle. The number of muscle fibers that are part of a motor unit corresponds to the precision of control of that muscle. Also, muscles that have finer motor control have more motor units connecting to them, and this requires a larger topographical field in the primary motor cortex.

Motor neuron axons connect to muscle fibers at a neuromuscular junction. This is a specialized synaptic structure at which multiple axon terminals synapse with the muscle fiber cell membrane. The terminal button of the motor neurons secrete acetylcholine, which binds to receptors on the sarcolemma. The binding of acetylcholine opens ligand-gated ion channels, increasing the movement of cations across the sarcolemma. This depolarizes the sarcolemma, initiating muscle contraction. Whereas other synapses result in graded potentials that must reach a threshold in the postsynaptic target, activity at the neuromuscular junction reliably leads to muscle fiber contraction with every nerve impulse received from a motor neuron. However, the strength of contraction and the number of fibers that contract can be affected by the frequency of the motor neuron impulses.

Chapter Review

The motor components of the somatic nervous system begin with the frontal lobe of the brain, where the prefrontal cortex is responsible for higher functions such as working memory. The integrative and associate functions of the prefrontal lobe feed into the secondary motor areas, which help plan movements. The premotor cortex and supplemental motor area then feed into the primary motor cortex that initiates movements. Large Betz cells

project through the corticobulbar and corticospinal tracts to synapse on lower motor neurons in the brain stem and ventral horn of the spinal cord, respectively. These connections are responsible for generating movements of skeletal muscles.

The extrapyramidal system includes projections from the brain stem and higher centers that influence movement, mostly to maintain balance and posture, as well as to maintain muscle tone. The superior colliculus and red nucleus in the midbrain, the vestibular nuclei in the medulla, and the reticular formation throughout the brain stem each have tracts projecting to the spinal cord in this system. Descending input from the secondary motor cortices, basal nuclei, and cerebellum connect to the origins of these tracts in the brain stem.

All of these motor pathways project to the spinal cord to synapse with motor neurons in the ventral horn of the spinal cord. These lower motor neurons are the cells that connect to skeletal muscle and cause contractions. These neurons project through the spinal nerves to connect to the muscles at neuromuscular junctions. One motor neuron connects to multiple muscle fibers within a target muscle. The number of fibers that are innervated by a single motor neuron varies on the basis of the precision necessary for that muscle and the amount of force necessary for that motor unit. The quadriceps, for example, have many fibers controlled by single motor neurons for powerful contractions that do not need to be precise. The extraocular muscles have only a small number of fibers controlled by each motor neuron because moving the eyes does not require much force, but needs to be very precise.

Glossary

pyramidal decussation

location at which corticospinal tract fibers cross the midline and segregate into the anterior and lateral divisions of the pathway

pyramids

segment of the descending motor pathway that travels in the anterior position of the medulla

OU Human Physiology: Reflexes By the end of this section, you will be able to:

- Identify the players in a reflex arc
- Explain the role of each player in a reflex arc
- Describe the withdrawal reflex
- Explain the muscle spindle stretch reflexes
- Classify reflexes according to the four groups

Reflexes

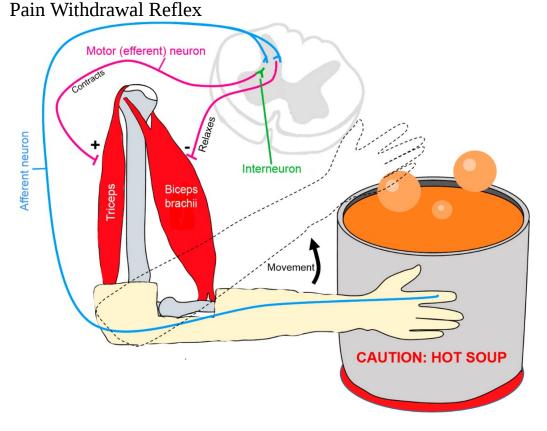
This chapter began by introducing reflexes. Reflexes are neural pathways involving patterned responses to a sensory stimulus. These neural pathways are often referred to as **reflex arcs** ([link]). In order to generate a reflex, there are several players that must coordinate their actions. These players include: a stimulus, sensory receptor, afferent neuron, integration center (CNS), efferent neuron, and an effector. To set this pathway in motion, the receptor must detect a stimulus; once detected an electrical signal will be sent along the afferent neuron to the CNS which will then decide on a response and send an electrical signal via the efferent neuron to the effector organ which brings about the desired response. If you remember the Latin root "effere" means "to carry"; adding the prefix "ef-" suggests the meaning "to carry away", whereas adding the prefix "af-" suggests "to carry toward or inward." Hence the afferent neuron will carry a signal toward the CNS and the efferent neuron will carry a signal away from the CNS.

Generalized Reflex Arc Schematic



Let's relate the components of the reflex arc to our example of the withdrawal reflex that you were introduced to at the beginning of this chapter.

When you touch a hot pot on a stove, you pull your hand away. How does the body know to do that? Sensory receptors in the skin sense extreme temperature. This triggers an action potential which travels along the sensory fiber from the skin, through the dorsal spinal root to the spinal cord, and directly activates a ventral horn motor neuron. That neuron sends a signal along its axon to excite the biceps brachii, causing contraction of the muscle and flexion of the forearm at the elbow to withdraw the hand from the hot stove. This is an excellent example of a reflex as it demonstrates a response that automatically occurs without any conscious effort ([link]).

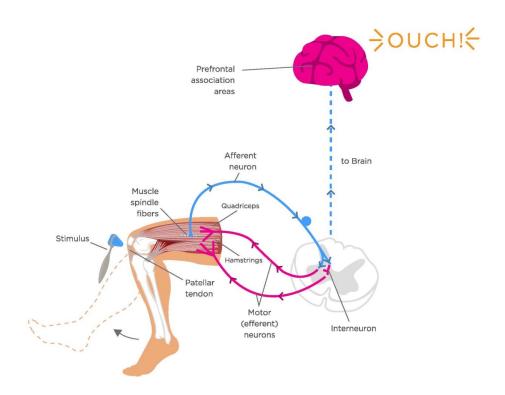


When a sensory receptor in the hand senses a hot object it sends a nerve impulse to the spinal cord which then sends a nerve impulse to relax the biceps brachii and to constrict the triceps to move the hand away from the painful stimulus.

Another type of reflex is a **stretch reflex**. In this reflex, when a skeletal muscle is stretched, a muscle spindle receptor is activated. These reflexes are commonly called muscle spindle stretch reflexes. The axon from this receptor structure will cause direct contraction of the muscle. A collateral of the muscle spindle fiber will also inhibit the motor neuron of the antagonist

muscles. The reflex helps to maintain muscles at a constant length. A common example of this muscle spindle stretch reflex is the knee jerk that is elicited by a rubber hammer struck against the patellar ligament in a physical exam. The players in the knee jerk reflex include: hammer (stimulus), muscle spindle (receptor that detects muscle lengthening), afferent neuron, spinal cord (integrator), efferent neuron, and the quadriceps muscle (effector). When a physician taps the patellar tendon on the knee with a hammer, the patellar tendon stretches which then stretches the quadriceps muscle. This stretch is detected by the muscle spindle receptor which responds by generating an action potential in the afferent neuron which synapses with the efferent neuron in the ventral horn of the spinal cord. An action potential is then generated along the efferent neuron that innervates the quadriceps muscle stimulating it to contract causing the leg to kick out ([link]).

Knee Jerk Reflex



Depicted in the diagram is the knee jerk reflex. When the patellar tendon is hit, it sends a signal to the spinal cord that travels back through a motor neuron without going to brain. The motor neuron starts the contraction of muscle spindle

fibers in the quadriceps to contract and the hamstrings to relax. However, if a patient expects the patellar hit a signal travels to the brain first (dotted line).

Like the withdrawal reflex, in order for the quadriceps to contract the hamstring must relax. This occurs because the afferent neurons have collaterals so while one efferent neuron is stimulating the quadriceps to contract another efferent neuron that synapsed with the same afferent neuron is inhibiting contraction of the hamstring muscle. To do this, the afferent neuron synapses with other neurons (an interneuron and an efferent neuron) in the spinal cord. The interneuron is inhibitory which inhibits the efferent neuron and therefore the hamstring. Thus, the hamstring will remain relaxed while the quadriceps contracts.

A specialized reflex to protect the surface of the eye is the **corneal reflex**, or the eye blink reflex. When the cornea is stimulated by a tactile stimulus, or even by bright light in a related reflex, blinking is initiated. The sensory component travels through the trigeminal nerve, which carries somatosensory information from the face, or through the optic nerve, if the stimulus is bright light. The motor response travels through the facial nerve and innervates the orbicularis oculi on the same side. This reflex is commonly tested during a physical exam using an air puff or a gentle touch of a cotton-tipped applicator.

All reflexes, including the withdrawal reflex, knee jerk reflex, and corneal reflex, can be classified into each of the following four groups.

- *Cranial or Spinal*. The level of processing will determine whether the reflex is cranial or spinal. If the highest level of integration is the brain, the reflex is cranial and if the reflex involves only the spinal cord it is a spinal reflex.
- *Autonomic or Somatic*. If the reflex involves the somatic nervous system and therefore skeletal muscle, the reflex will be characterized as somatic, but if the reflex involves the autonomic nervous system

- and therefore cardiac muscle or smooth muscle, the reflex will be characterized as autonomic.
- *Monosynaptic, Disynaptic, or Polysynaptic.* These reflexes are characterized as to the number of synapses in the reflex. Remember to study those prefixes (mono- means one, di- means two, and polymeans many). If there is only one synapse (mono-) which means there are two neurons involved, this reflex is characterized as a monosynaptic reflex. If there are two synapses, there are four neurons involved and this reflex is characterized as disynaptic. If there are more than two synapses which implies there are more than four neurons, the reflex is polysynaptic.
- *Innate or Conditioned*. If the reflex is innate you are born with this reflex. We are all born with innate reflexes. Conditioned reflexes are ones that we have trained based on our life experiences. Olympic divers have to condition the reflex that causes them to stick their head out when they dive off a diving board so they have to focus on training that reflex and tucking the head in; otherwise a belly flop is inevitable.

Note:



Watch this <u>video</u> to learn more about the reflex arc of the corneal reflex. When the right cornea senses a tactile stimulus, what happens to the left eye? Explain your answer.

Note:			



Watch this <u>video</u> to learn more about newborn reflexes. Newborns have a set of reflexes that are expected to have been crucial to survival before the modern age. These reflexes disappear as the baby grows, as some of them may be unnecessary as they age. The video demonstrates a reflex called the Babinski reflex, in which the foot flexes dorsally and the toes splay out when the sole of the foot is lightly scratched. This is normal for newborns, but it is a sign of reduced myelination of the spinal tract in adults. Why would this reflex be a problem for an adult?

Chapter Review

Reflexes are the simplest circuits within the somatic nervous system. A withdrawal reflex from a painful stimulus only requires the sensory fiber that enters the spinal cord and the motor neuron that projects to a muscle. Antagonist and postural muscles can be coordinated with the withdrawal, making the connections more complex. The simple, single neuronal connection is the basis of somatic reflexes. The corneal reflex is contraction of the orbicularis oculi muscle to blink the eyelid when something touches the surface of the eye. Stretch reflexes maintain a constant length of muscles by causing a contraction of a muscle to compensate for a stretch that can be sensed by a specialized receptor called a muscle spindle.

Glossary

corneal reflex

protective response to stimulation of the cornea causing contraction of the orbicularis oculi muscle resulting in blinking of the eye

reflex arc

pathway by which a stimulus reflexively induces a response

stretch reflex

response to activation of the muscle spindle stretch receptor that causes contraction of the muscle to maintain a constant length

OU Human Physiology: Introduction to the Autonomic Nervous System class="introduction" Fight or Flight?

```
Though the
threats that
 modern
 humans
face are not
   large
predators,
    the
autonomic
 nervous
 system is
adapted to
this type of
 stimulus.
   The
 modern
  world
 presents
stimuli that
trigger the
   same
response.
  (credit:
  Vernon
Swanepoel
     )
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Note:

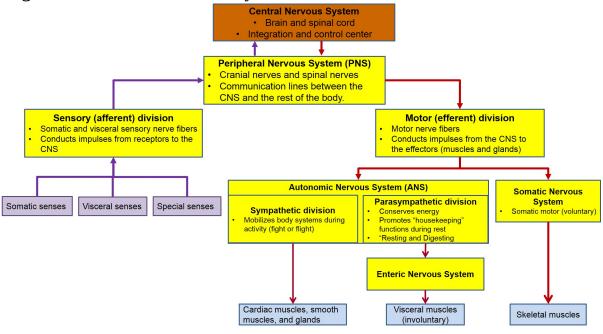
Chapter Objectives

After studying this chapter, you will be able to:

- Describe the components of the autonomic nervous system.
- Describe the anatomy of the autonomic nervous system
- Explain dual innervation
- Compare and contrast preganglionic and postganglionic nerve fibers for the two divisions of the autonomic nervous system in terms of neurotransmitters, hormones, receptors, target cells and the target cell response
- Describe the players and their role in a reflex arc
- Determine the effect of the autonomic nervous system on the regulation of the various organ systems on the basis of the signaling molecules involved
- Describe how the central nervous system coordinates and contributes to autonomic functions

The autonomic nervous system is part of the efferent division of the peripheral nervous system ([link]). The autonomic nervous system is often associated with the "fight-or-flight response," which refers to the preparation of the body to either run away from a threat or to stand and fight in the face of that threat. To suggest what this means, consider the (very unlikely) situation of seeing a lioness hunting out on the savannah. Though this is not a common threat that humans deal with in the modern world, it represents the type of environment in which the human species thrived and adapted. The spread of humans around the world to the present state of the modern age occurred much more quickly than any species would adapt to environmental pressures such as predators. However, the reactions modern humans have in the modern world are based on these prehistoric situations. If your boss is walking down the hallway on Friday afternoon looking for "volunteers" to come in on the weekend, your response is the same as the prehistoric human seeing the lioness running across the savannah: fight or flight.

Organization of the Nervous System



Most likely, your response to your boss—not to mention the lioness—would be flight. Run away! The autonomic system is responsible for the physiological response to make that possible, and hopefully successful. Adrenaline starts to flood your circulatory system. Your heart rate increases. Sweat glands become active. The bronchi of the lungs dilate to allow more

air exchange. Pupils dilate to increase visual information. Blood pressure increases in general, and blood vessels dilate in skeletal muscles. Time to run. Similar physiological responses would occur in preparation for fighting off the threat.

This response should sound a bit familiar. The autonomic nervous system is tied into emotional responses as well, and the fight-or-flight response probably sounds like a panic attack. In the modern world, these sorts of reactions are associated with anxiety as much as with response to a threat. It is engrained in the nervous system to respond like this. In fact, the adaptations of the autonomic nervous system probably predate the human species and are likely to be common to all mammals, and perhaps shared by many animals. That lioness might herself be threatened in some other situation.

However, the autonomic nervous system is not just about responding to threats. Besides the fight-or-flight response, there are the responses referred to as "rest and digest." If that lioness is successful in her hunting, then she is going to rest from the exertion. Her heart rate will slow. Breathing will return to normal. The digestive system has a big job to do. Much of the function of the autonomic system is based on the connections within an autonomic, or visceral, reflex.

OU Human Physiology: Divisions of the Autonomic Nervous System By the end of this section, you will be able to:

- Name the components that generate the sympathetic and parasympathetic responses of the autonomic nervous system
- Describe the anatomy of the autonomic nervous system
- Explain dual innervation within the autonomic nervous system and provide examples
- Describe the mechanism for acetylcholine and catecholamine degradation
- Explain neurotransmitter release from varicosities
- Explain the anatomical differences in output connections within the two divisions of the autonomic nervous system
- Identify the neurotransmitters, hormones, and receptor proteins involved in communication within the two divisions of the autonomic nervous system
- Infer where neurotransmitter binding to target receptor will generate a fast or slow response

The nervous system can be divided into two functional parts: the somatic nervous system and the autonomic nervous system. The major differences between the two systems are evident in the responses that each produces. The somatic nervous system causes contraction of skeletal muscles. The autonomic nervous system controls cardiac and smooth muscle, as well as glandular tissue. The somatic nervous system is associated with voluntary responses (though many can happen without conscious awareness, like breathing), and the autonomic nervous system is associated with involuntary responses, such as those related to homeostasis.

The autonomic nervous system regulates many of the internal organs through a balance of two aspects, or divisions. In addition to the endocrine system, the autonomic nervous system is instrumental in homeostatic mechanisms in the body. The two divisions of the autonomic nervous system are the **sympathetic division** and the **parasympathetic division**. The sympathetic system is associated with periods of stress or physical activity like those of a **fight-or-flight response**, and parasympathetic activity is referred to by the epithet of **rest and digest** or the "fat and happy system." This division is most active during periods of rest. Homeostasis is the balance between the two systems when the activity of one division increases the other decreases. At each target effector, dual innervation determines activity. For example, the heart receives connections from both the sympathetic and parasympathetic divisions. One causes heart rate to increase, whereas the other causes heart rate to decrease. Thus dual innervation means one organ is innervated by nerve fibers of the sympathetic and parasympathetic divisions. Many organs are dually innervated, but not all organs.

Note:

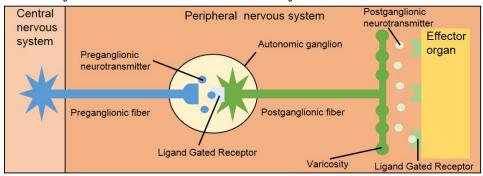


Watch this <u>video</u> to learn more about adrenaline and the fight-or-flight response. When someone is said to have a rush of adrenaline, the image of bungee jumpers or skydivers usually comes to mind. But adrenaline, also known as epinephrine, is an important chemical in coordinating the body's fight-or-flight response. In this video, you look inside the physiology of the fight-or-flight response, as envisioned for a firefighter. His body's reaction is the result of the sympathetic division of the autonomic nervous system causing system-wide changes as it prepares for extreme responses. What two changes does adrenaline bring about to help the skeletal muscle response?

Anatomy of the Autonomic Nervous System

The autonomic nervous system provides communication between the central nervous system and the effector organs ([link]). This involves two neurons, a **preganglionic fiber** (also called a preganglionic neuron) and a **postganglionic fiber** (also called postganglionic neuron) that synapse at a location called the **autonomic ganglion**. The preganglionic fibers travel from the CNS to the autonomic ganglia while the postganglionic fibers extend from the autonomic ganglia to the effectors. Both the cell bodies and dendrites of the preganglionic fiber are located within the central nervous system while the axon and axon terminals are in the peripheral nervous system. The axon terminals of these preganglionic fibers are part of the autonomic ganglia that release neurotransmitters that bind to ligand gated receptors on the dendrites or cell bodies of the postganglionic fiber which are also part of the autonomic ganglia. All neuronal structures of the postganglionic fiber are located in the peripheral nervous system. The postganglionic fiber has varicosities at the terminal end of the axon which release neurotransmitters. When these neurotransmitters are released they will bind to ligand gated channels on the effector organs. Effectors in the ANS include cardiac and smooth muscle as well as glands, and adipose tissue. This synapse between the postsynaptic fiber and an effector is called a neuroeffector junction.

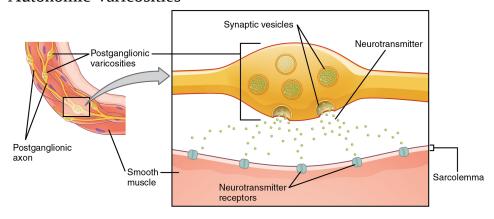
Anatomy of the Autonomic Nervous System



A generalized connection between the central nervous system and the target effectors via the peripheral nervous system.

The **varicosities** of postganglionic fibers are similar in function to axon terminals as they too release neurotransmitters, but they are structurally very different ([link]). Varicosities can be described as swellings along the terminal portion of the axon rather than one discrete axon terminal. The varicosities synthesize, store, and release neurotransmitters much like axon terminals; hence varicosities contain voltage gated calcium channels. When the postganglionic fiber is depolarized this will stimulate the opening of the voltage gated calcium channels and calcium influx will take place. This influx of calcium will stimulate the exocytosis of the neurotransmitters into the cleft. The neurotransmitters will then bind to the ligand gated channel on the effector causing a cell response

Autonomic Varicosities



The connection between autonomic fibers and target effectors is not the same as the typical synapse, such as the neuromuscular junction. Instead of a synaptic end bulb, a neurotransmitter is released from swellings along the length of a fiber that makes an extended network of connections in the target effector.

Just like neurotransmitters released by discrete axon terminals, the neurotransmitters in the ANS must be removed from the neuroeffector junction. The mechanism for this is similar to those already discussed for a neuron-to-neuron synapse. These may include diffusion of the neurotransmitter from the effector, reuptake of the neurotransmitter, or enzymatic degradation. Acetylcholine and catecholamines are very common neurotransmitters in the human body. We have already discussed these neurotransmitters in the Synaptic Transmission Neural Integration reading; however, we have spent little time discussing their degradation.

Acetylcholine degradation.

The neurotransmitter **acetylcholine** (**ACh**) is degraded by the enzyme called **acetylcholinesterase** (**AChE**). This enzyme is located on the membrane of the cell body/dendrites of the postganglionic neuron and effector organs at cholinergic neuroeffector junctions. When acetylcholine binds to acetylcholinesterase, acetylcholine is degraded into choline and acetate. Choline is actively transported back into the preganglionic fiber and postganglionic varicosity via reuptake and used to make more acetylcholine. Acetate will diffuse away from the synapse.

Catecholamine degradation.

Catecholamines include epinephrine, norepinephrine, and dopamine. These are degraded by an enzyme called **monoamine oxidase (MAO)** which is located within the mitochondria of postganglionic neurons at adrenergic neuroeffector junctions. Catecholamines are actively transported via reuptake into the postganglionic mitochondria where they are then degraded.

Sympathetic Division of the Autonomic Nervous System

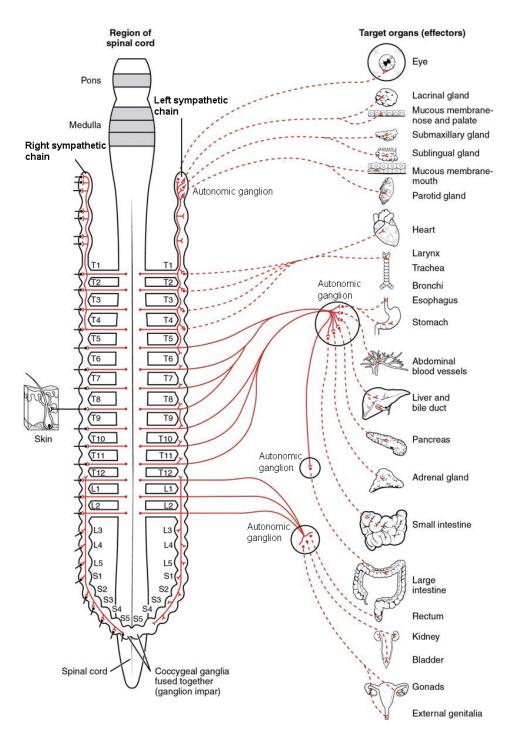
To respond to a threat—to fight or to run away—the sympathetic system causes divergent effects as many different effector organs are activated together for a common purpose. More oxygen needs to be inhaled and delivered to skeletal muscle. The respiratory, cardiovascular, and musculoskeletal systems are all activated together. Additionally, sweating keeps the excess heat that comes from

muscle contraction from causing the body to overheat. The digestive system shuts down so that blood is not absorbing nutrients when it should be delivering oxygen to skeletal muscles. To coordinate all these responses, the connections in the sympathetic system diverge from a limited region of the central nervous system (CNS) to a wide array of ganglia that project to the many effector organs simultaneously. The complex set of structures that compose the output of the sympathetic system make it possible for these disparate effectors to come together in a coordinated, systemic change.

The sympathetic division of the autonomic nervous system influences the various organ systems of the body through connections emerging from the thoracic and upper lumbar spinal cord. It is referred to as the **thoracolumbar system** to reflect this anatomical basis. For this reason the nerves of the sympathetic division are often referred to as thoracolumbar nerves. A **central neuron** in the lateral horn of any of these spinal regions projects to ganglia adjacent to the vertebral column through the ventral spinal roots. The majority of ganglia of the sympathetic system belong to a network of **sympathetic chain ganglia** that runs alongside the vertebral column. The ganglia appear as a series of clusters of neurons linked by axonal bridges. There are typically 23 ganglia in the chain on either side of the spinal column. Three correspond to the cervical region, 12 are in the thoracic region, four are in the lumbar region, and four correspond to the sacral region. The cervical and sacral levels are not connected to the spinal cord directly through the spinal roots, but through ascending or descending connections through the bridges within the chain.

A diagram that shows the connections of the sympathetic system is somewhat like a circuit diagram that shows the electrical connections between different receptacles and devices. In [link], the "circuits" of the sympathetic system are intentionally simplified.

Connections of Sympathetic Division of the Autonomic Nervous System



Neurons from the lateral horn of the spinal cord (preganglionic neurons) project to the chain ganglia on either side of the vertebral column or to collateral (prevertebral) ganglia that are anterior to the vertebral column in the abdominal cavity. Axons from these

ganglionic neurons (postganglionic fibers) then project to target effectors throughout the body.

To continue with the analogy of the circuit diagram, there are three different types of "junctions" that operate within the sympathetic system ([link]). The first type is most direct: the sympathetic nerve projects to the chain ganglion at the same level as the **target effector** (the organ, tissue, or gland to be innervated). An example of this type is spinal nerve T1 that synapses with the T1 chain ganglion to innervate the trachea. The fibers of this branch are called white rami communicantes (singular = ramus communicans); they are myelinated and therefore referred to as white (see [link]a). The axon from the central neuron (the preganglionic fiber shown as a solid line) synapses with the ganglionic neuron (with the postganglionic fiber shown as a dashed line). This neuron then projects to a target effector—in this case, the trachea—via gray rami communicantes, which are unmyelinated axons.

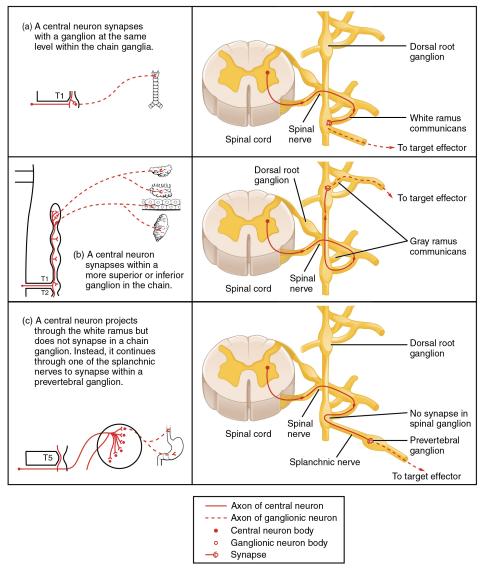
In some cases, the target effectors are located superior or inferior to the spinal segment at which the preganglionic fiber emerges. With respect to the "wiring" involved, the synapse with the ganglionic neuron occurs at chain ganglia superior or inferior to the location of the central neuron. An example of this is spinal nerve T1 that innervates the eye. The spinal nerve tracks up through the chain until it reaches the superior cervical ganglion, where it synapses with the postganglionic neuron (see [link]b). The cervical ganglia are referred to as paravertebral ganglia, given their location adjacent to prevertebral ganglia in the sympathetic chain.

Not all axons from the central neurons terminate in the chain ganglia. Additional branches from the ventral nerve root continue through the chain and on to one of the collateral ganglia as the greater splanchnic nerve or lesser splanchnic nerve. For example, the greater splanchnic nerve at the level of T5 synapses with a collateral ganglion outside the chain before making the connection to the postganglionic nerves that innervate the stomach (see [link]c).

Collateral ganglia, also called prevertebral ganglia, are situated anterior to the vertebral column and receive inputs from splanchnic nerves as well as central sympathetic neurons. They are associated with controlling organs in the abdominal cavity, and are also considered part of the enteric nervous system. The three collateral ganglia are the celiac ganglion, the superior mesenteric ganglion, and the inferior mesenteric ganglion (see [link]). The word celiac is derived from the Latin

word "coelom," which refers to a body cavity (in this case, the abdominal cavity), and the word mesenteric refers to the digestive system.

Sympathetic Connections and Chain Ganglia

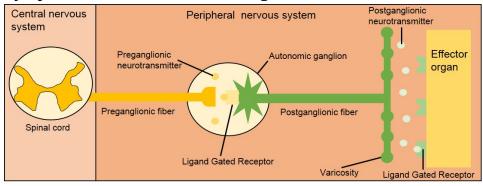


The axon from a central sympathetic neuron in the spinal cord can project to the periphery in a number of different ways. (a) The fiber can project out to the ganglion at the same level and synapse on a ganglionic neuron. (b) A branch can project to more superior or inferior ganglion in the chain. (c) A branch can project through the white ramus communicans, but not terminate on a ganglionic neuron in the chain. Instead, it projects through one of the splanchnic

nerves to a collateral ganglion or the adrenal medulla (not pictured).

An axon from the central neuron that projects to a sympathetic ganglion is referred to as a **preganglionic fiber** or neuron, and represents the output from the CNS to the ganglion [link]. Because the sympathetic ganglia are adjacent to the vertebral column, preganglionic sympathetic fibers are relatively short, and they are myelinated. A **postganglionic fiber**—the axon from a ganglionic neuron that projects to the target effector—represents the output of a ganglion that directly influences the organ. Compared with the preganglionic fibers, postganglionic sympathetic fibers are long because of the relatively greater distance from the ganglion to the target effector. These fibers are unmyelinated. (Note that the term "postganglionic neuron" may be used to describe the projection from a ganglion to the target. The problem with that usage is that the cell body is in the ganglion, and only the fiber is postganglionic. Typically, the term neuron applies to the entire cell.)

Sympathetic Connection to the Target Effector

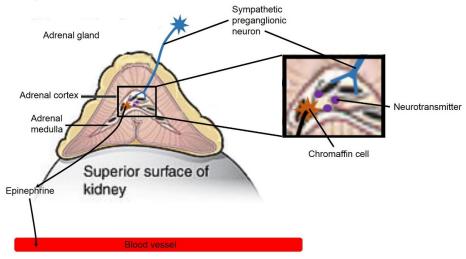


A preganglionic fiber projects from the lateral horn of the spinal cord and enters the sympathetic ganglion where it synapses with a postganglionic fiber which then goes to the target effector.

One type of preganglionic sympathetic fiber does not terminate in a ganglion. These are the axons from central sympathetic neurons that project to the **adrenal medulla**, the interior portion of the adrenal gland. These axons are still referred to as preganglionic fibers, but the postganglionic fibers are modified and are called **chromaffin cells**. When stimulated these neurosecretory chromaffin cells of the

adrenal medulla release primarily epinephrine, but also norepinephrine and dopamine into the bloodstream. These messengers act as hormones since they are traveling via the blood to target tissue.

Sympathetic Innervation of the Adrenal Gland



The sympathetic nervous system innervates the adrenal medulla. The preganglionic neuron secretes acetylcholine which bind to receptors on chromaffin cells stimulating the synthesis and secretion of mostly epinephrine.

The projections of the sympathetic division of the autonomic nervous system diverge widely, resulting in a broad influence of the system throughout the body. As a response to a threat, the sympathetic system would increase heart rate and breathing rate and cause blood flow to the skeletal muscle to increase and blood flow to the digestive system to decrease. Sweat gland secretion should also increase as part of an integrated response. All of those physiological changes are going to be required to occur together to run away from the hunting lioness, or the modern equivalent. This divergence is seen in the branching patterns of preganglionic sympathetic neurons—a single preganglionic sympathetic neuron may have 10–20 targets. An axon that leaves a central neuron of the lateral horn in the thoracolumbar spinal cord will pass through the white ramus communicans and enter the sympathetic chain, where it will branch toward a variety of targets. At the level of the spinal cord at which the preganglionic sympathetic fiber exits the spinal cord, a branch will synapse on a neuron in the adjacent chain ganglion. Some branches will extend up or down to a different level of the chain ganglia. Other branches will pass through the chain ganglia and project through one of the

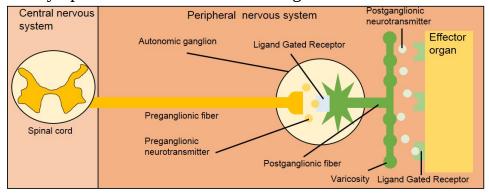
splanchnic nerves to a collateral ganglion. Finally, some branches may project through the splanchnic nerves to the adrenal medulla. All of these branches mean that one preganglionic neuron can influence different regions of the sympathetic system very broadly, by acting on widely distributed organs.

Parasympathetic Division of the Autonomic Nervous System

The parasympathetic division of the autonomic nervous system is named because its central neurons are located on either side of the thoracolumbar region of the spinal cord (para- = "beside" or "near"). The parasympathetic system can also be referred to as the **craniosacral system** (or outflow) because the preganglionic neurons are located in nuclei of the brain stem and the lateral horn of the sacral spinal cord. For this reason the nerves of the parasympathetic division are often referred to as craniosacral nerves.

The connections, or "circuits," of the parasympathetic division are similar to the general layout of the sympathetic division with a few specific differences ([link]). The preganglionic fibers from the cranial region travel in cranial nerves, whereas preganglionic fibers from the sacral region travel in spinal nerves. The targets of these fibers are **terminal ganglia**, which are located near—or even within—the target effector. These ganglia are often referred to as **intramural ganglia** when they are found within the walls of the target organ. The postganglionic fiber projects from the terminal ganglia a short distance to the target effector, or to the specific target tissue within the organ. Comparing the relative lengths of axons in the parasympathetic system, the preganglionic fibers are long and the postganglionic fibers are short because the ganglia are close to—and sometimes within—the target effectors ([link]).

Parasympathetic Connection to the Target Effector

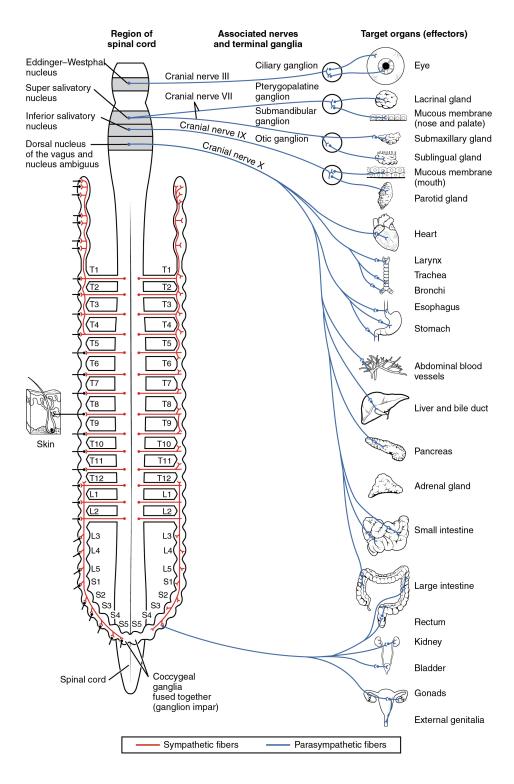


A preganglionic fiber projects from the lateral horn of the spinal cord and enters the parasympathetic ganglion where

it synapses with a postganglionic fiber which then goes to the target effector.

The cranial component of the parasympathetic system is based in particular nuclei of the brain stem. In the midbrain, the **Eddinger–Westphal nucleus** is part of the oculomotor complex, and axons from those neurons travel with the fibers in the oculomotor nerve (cranial nerve III) that innervate the extraocular muscles. The preganglionic parasympathetic fibers within cranial nerve III terminate in the **ciliary ganglion**, which is located in the posterior orbit. The postganglionic parasympathetic fibers then project to the smooth muscle of the iris to control pupillary size. In the upper medulla, the salivatory nuclei contain neurons with axons that project through the facial and glossopharyngeal nerves to ganglia that control salivary glands. Tear production is influenced by parasympathetic fibers in the facial nerve, which activate a ganglion, and ultimately the lacrimal (tear) gland. Neurons in the **dorsal nucleus of the vagus nerve** and the **nucleus ambiguus** project through the vagus nerve (cranial nerve X) to the terminal ganglia of the thoracic and abdominal cavities. Parasympathetic preganglionic fibers primarily influence the heart, bronchi, and esophagus in the thoracic cavity and the stomach, liver, pancreas, gall bladder, and small intestine of the abdominal cavity. The postganglionic fibers from the ganglia activated by the vagus nerve are often incorporated into the structure of the organ, such as the **mesenteric plexus** of the digestive tract organs and the intramural ganglia.

Connections of Parasympathetic Division of the Autonomic Nervous System



Neurons from brain-stem nuclei, or from the lateral horn of the sacral spinal cord, project to terminal ganglia near or within the various organs of the body. Axons from these ganglionic neurons then project the short distance to those target effectors.

Chemical Signaling in the Autonomic Nervous System

When the autonomic nervous system is stimulated and depolarization spreads down the axon, be it a pre- or postganglionic axon, the change in the membrane potential will stimulate the voltage gated calcium channels, located in the membrane of the axon terminal to open. As a result, calcium influx will occur stimulating the exocytosis of a neurotransmitter. Where an autonomic neuron connects with an effector, there is a synapse called the neuroeffector junction. Synapses of the autonomic system are classified as either **cholinergic**, meaning that **acetylcholine** (**ACh**) is released, or **adrenergic**, meaning that **norepinephrine** is released. The terms cholinergic and adrenergic refer not only to the signaling molecule that is released but also to the class of receptors that each binds.

The cholinergic system includes two classes of receptor: the **nicotinic receptor** and the **muscarinic receptor**. Both receptor types bind to ACh. Nicotinic cholinergic receptor is a ligand gated channel and is located on the membrane of the cell bodies and dendrites of postsynaptic neurons. The muscarinic cholinergic receptor is a **G** protein coupled receptor located on the membrane of the effector organ. When stimulated this G protein may cause direct coupling or stimulate a second messenger system. The receptors are named for, and differentiated by, other molecules that bind to them. Whereas nicotine will bind to the nicotinic receptor, and muscarine will bind to the muscarinic receptor, there is no crossreactivity between the receptors. The situation is similar to locks and keys. Imagine two locks—one for a classroom and the other for an office—that are opened by two separate keys. The classroom key will not open the office door and the office key will not open the classroom door. This is similar to the specificity of nicotine and muscarine for their receptors. However, a master key can open multiple locks, such as a master key for the Biology Department that opens both the classroom and the office doors. This is similar to ACh that binds to both types of receptors. The molecules that define these receptors are not crucial—they are simply tools for researchers to use in the laboratory. These molecules are **exogenous**, meaning that they are made outside of the human body, so a researcher can use them without any confounding **endogenous** results (results caused by the molecules produced in the body).

The adrenergic system also has two types of receptors, named the **alpha** (α)-adrenergic receptor and **beta** (β)-adrenergic receptor all of which are located on the membrane of effector organs. Unlike cholinergic receptors, these receptor types are not classified by which drugs can bind to them. All of them are G protein—coupled receptors that either activate or inhibit second messenger systems. There are two types of α -adrenergic receptors, termed α_1 and α_2 , and there are three types of β -adrenergic receptors, termed β_1 , β_2 , and β_3 . [link] compares and contrasts these receptor types. Both epinephrine and norepinephrine can bind to these adrenergic receptors however, some receptors have varying affinities for these ligands as illustrated. The chemical difference between norepinephrine and epinephrine is the addition of a methyl group (CH₃) in epinephrine. The prefix "nor-" actually refers to this chemical difference, in which a methyl group is missing.

Receptor type	Effector organ with receptor type	Relative affinities *	Signal transduction mechanism	Effect on effector organ
α_1	Most vascular smooth muscle, pupils	NE > Epi	Activates IP ₃	Excitatory
α_2	CNS, platelets, adrenergic nerve (autoreceptors), some vascular smooth muscle, adipose tissue	NE > Epi	Inhibits cAMP	Excitatory
eta_1	CNS, cardiac muscle, kidney	NE = Epi	Activates cAMP	Excitatory
β_2	Smooth blood vessels,	Epi >> NE	Activates cAMP	Inhibitory

	respiratory tract, uterus			
β_3	Adipose tissue	NE = Epi	Activates cAMP	Exitatory

Adrenergic Receptors* NE = norepinephrine; Epi = epinephrine; > = greater than; >> = much greater than

The term adrenergic should remind you of the word adrenaline, which is associated with the fight-or-flight response described at the beginning of the chapter. Adrenaline and epinephrine are two names for the same molecule. The adrenal gland (in Latin, ad- = "on top of"; renal = "kidney") secretes adrenaline. The ending "-ine" refers to the chemical being derived, or extracted, from the adrenal gland. A similar construction from Greek instead of Latin results in the word epinephrine (epi- = "above"; nephr- = "kidney"). In scientific usage, epinephrine is preferred in the United States, whereas adrenaline is preferred in Great Britain, because "adrenalin" was once a registered, proprietary drug name in the United States. Though the drug is no longer sold, the convention of referring to this molecule by the two different names persists. Similarly, norepinephrine and noradrenaline are two names for the same molecule.

Having understood the cholinergic and adrenergic systems, their role in the autonomic system is relatively simple to understand. All preganglionic fibers, both sympathetic and parasympathetic, release ACh. All ganglionic neurons—the targets of these preganglionic fibers—have nicotinic receptors in their cell membranes. The nicotinic receptor is a ligand-gated cation channel that results in depolarization of the postsynaptic membrane. The postganglionic parasympathetic fibers also release ACh, but the receptors on their targets are muscarinic receptors, which are G protein—coupled receptors and do not exclusively cause depolarization of the postsynaptic membrane. Postganglionic sympathetic fibers release norepinephrine, except for fibers that project to sweat glands and to blood vessels associated with skeletal muscles, which release ACh ([link]).

Autonomic System Signaling Molecules

Autonomic Syste	m SignalingeMo lecules	Parasympathetic
	Sympathetic	Parasympathetic
Preganglionic	Acetylcholine → nicotinic receptor	Acetylcholine → nicotinic receptor
Postganglionic	Norepinephrine → α- or β- adrenergic receptors Acetylcholine → muscarinic receptor (associated with sweat glands and the blood vessels associated with skeletal muscles only	Acetylcholine → muscarinic receptor

Signaling molecules can belong to two broad groups. Neurotransmitters are released at synapses, whereas hormones are released into the bloodstream. These are simplistic definitions, but they can help to clarify this point. Acetylcholine can be considered a neurotransmitter because it is released by axons at synapses. The adrenergic system, however, presents a challenge. Postganglionic sympathetic fibers release norepinephrine, which can be considered a neurotransmitter. But the adrenal medulla releases epinephrine and norepinephrine into circulation, so they should be considered hormones.

Note:

Everyday Connections

Fight or Flight? What About Fright and Freeze?

The original usage of the epithet "fight or flight" comes from a scientist named Walter Cannon who worked at Harvard in 1915. The concept of homeostasis and the functioning of the sympathetic system had been introduced in France in the previous century. Cannon expanded the idea, and introduced the idea that an animal responds to a threat by preparing to stand and fight or run away. The nature of this response was thoroughly explained in a book on the physiology of pain, hunger, fear, and rage.

When students learn about the sympathetic system and the fight-or-flight response, they often stop and wonder about other responses. If you were faced with a lioness running toward you as pictured at the beginning of this chapter,

would you run or would you stand your ground? Some people would say that they would freeze and not know what to do. So isn't there really more to what the autonomic system does than fight, flight, rest, or digest. What about fear and paralysis in the face of a threat?

The common epithet of "fight or flight" is being enlarged to be "fight, flight, or fright" or even "fight, flight, fright, or freeze." Cannon's original contribution was a catchy phrase to express some of what the nervous system does in response to a threat, but it is incomplete. The sympathetic system is responsible for the physiological responses to emotional states. The name "sympathetic" can be said to mean that (sym- = "together"; -pathos = "pain," "suffering," or "emotion").

Note:



Watch this <u>video</u> to learn more about the nervous system. As described in this video, the nervous system has a way to deal with threats and stress that is separate from the conscious control of the somatic nervous system. The system comes from a time when threats were about survival, but in the modern age, these responses become part of stress and anxiety. This video describes how the autonomic system is only part of the response to threats, or stressors. What other organ system gets involved, and what part of the brain coordinates the two systems for the entire response, including epinephrine (adrenaline) and cortisol?

Chapter Review

The primary responsibilities of the autonomic nervous system are to regulate homeostatic mechanisms in the body, which is also part of what the endocrine system does. The key to understanding the autonomic system is to explore the response pathways—the output of the nervous system. The way we respond to the world around us, to manage the internal environment on the basis of the external environment, is divided between two parts of the autonomic nervous system. The sympathetic division responds to threats and produces a readiness to confront the

threat or to run away: the fight-or-flight response. The parasympathetic division plays the opposite role. When the external environment does not present any immediate danger, a restful mode descends on the body, and the digestive system is more active.

The sympathetic output of the nervous system originates out of the lateral horn of the thoracolumbar spinal cord. An axon from one of these central neurons projects by way of the ventral spinal nerve root and spinal nerve to a sympathetic ganglion, either in the sympathetic chain ganglia or one of the collateral locations, where it synapses on a ganglionic neuron. These preganglionic fibers release ACh, which excites the postganglionic neuron through the nicotinic receptor. The axon from the postganglionic neuron then projects to a target effector where it will release norepinephrine to bind to an adrenergic receptor, causing a change in the physiology of that organ in keeping with the broad, divergent sympathetic response. The postganglionic connections to sweat glands in the skin and blood vessels supplying skeletal muscle are, however, exceptions; those fibers release ACh onto muscarinic receptors. The sympathetic system has a specialized preganglionic connection to the modified postganglionic cells called chromaffin cells of the adrenal medulla that causes epinephrine and norepinephrine to be released into the bloodstream rather than exciting a neuron that contacts an organ directly. This hormonal component means that the sympathetic chemical signal can spread throughout the body very quickly and can affect many organ systems at once.

The parasympathetic output is based in the brain stem and sacral spinal cord. Neurons from particular nuclei in the brain stem or from the lateral horn of the sacral spinal cord (preganglionic neurons) project to terminal (intramural) ganglia located close to or within the wall of target effectors. These preganglionic fibers also release ACh onto nicotinic receptors to excite the postganglionic neurons. The postganglionic fibers then contact the target tissues within the organ to release ACh, which binds to muscarinic receptors to induce rest-and-digest responses.

Signaling molecules utilized by the autonomic nervous system are released from axons and can be considered as either neurotransmitters (when they directly interact with the effector) or as hormones (when they are released into the bloodstream). The same molecule, such as norepinephrine, could be considered either a neurotransmitter or a hormone on the basis of whether it is released from a postganglionic sympathetic axon or from the adrenal gland. The synapses in the autonomic system are not always the typical type of connection first described in the neuromuscular junction. Instead of having synaptic end bulbs at the very end

of an axonal fiber, they have swellings—called varicosities—along the length of a fiber so that it makes a network of connections within the target tissue.

Glossary

acetylcholine (ACh)

neurotransmitter that binds at a motor end-plate to trigger depolarization

acetylcholinesterase (AChE) (

an enzyme that degrades acetylcholine

adrenal medulla

interior portion of the adrenal (or suprarenal) gland that releases epinephrine and norepinephrine into the bloodstream as hormones

adrenergic

synapse where norepinephrine is released, which binds to α - or β -adrenergic receptors

alpha (α)-adrenergic receptor

one of the receptors to which epinephrine and norepinephrine bind, which comes in three subtypes: α_1 , α_2 , and α_3

autonomic ganglion

cluster of synapses between preganglionic and postganglionic neurons of the autonomic nervous system

beta (β)-adrenergic receptor

one of the receptors to which epinephrine and norepinephrine bind, which comes in two subtypes: β_1 and β_2

central neuron

specifically referring to the cell body of a neuron in the autonomic system that is located in the central nervous system, specifically the lateral horn of the spinal cord or a brain stem nucleus

cholinergic

synapse at which acetylcholine is released and binds to the nicotinic or muscarinic receptor

chromaffin cells

neuroendocrine cells of the adrenal medulla that release epinephrine and norepinephrine into the bloodstream as part of sympathetic system activity

ciliary ganglion

one of the terminal ganglia of the parasympathetic system, located in the posterior orbit, axons from which project to the iris

craniosacral system

alternate name for the parasympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in brainstem nuclei and the lateral horn of the sacral spinal cord; also referred to as craniosacral outflow

dorsal nucleus of the vagus nerve

location of parasympathetic neurons that project through the vagus nerve to terminal ganglia in the thoracic and abdominal cavities

Eddinger–Westphal nucleus

location of parasympathetic neurons that project to the ciliary ganglion

endogenous

describes substance made in the human body

epinephrine

signaling molecule released from the adrenal medulla into the bloodstream as part of the sympathetic response

exogenous

describes substance made outside of the human body

fight-or-flight response

set of responses induced by sympathetic activity that lead to either fleeing a threat or standing up to it, which in the modern world is often associated with anxious feelings

G protein-coupled receptor

membrane protein complex that consists of a receptor protein that binds to a signaling molecule—a G protein—that is activated by that binding and in turn activates an effector protein (enzyme) that creates a second-messenger molecule in the cytoplasm of the target cell

intramural ganglia

terminal ganglia of the parasympathetic system that are found within the walls of the target effector

mesenteric plexus

nervous tissue within the wall of the digestive tract that contains neurons that are the targets of autonomic preganglionic fibers and that project to the smooth muscle and glandular tissues in the digestive organ

muscarinic receptor

type of acetylcholine receptor protein that is characterized by also binding to muscarine and is a metabotropic receptor

nicotinic receptor

type of acetylcholine receptor protein that is characterized by also binding to nicotine and is an ionotropic receptor

norepinephrine

signaling molecule released as a neurotransmitter by most postganglionic sympathetic fibers as part of the sympathetic response, or as a hormone into the bloodstream from the adrenal medulla

nucleus ambiguus

brain-stem nucleus that contains neurons that project through the vagus nerve to terminal ganglia in the thoracic cavity; specifically associated with the heart

parasympathetic division

division of the autonomic nervous system responsible for restful and digestive functions

postganglionic fiber

axon from a ganglionic neuron in the autonomic nervous system that projects to and synapses with the target effector; sometimes referred to as a postganglionic neuron

preganglionic fiber

axon from a central neuron in the autonomic nervous system that projects to and synapses with a ganglionic neuron; sometimes referred to as a preganglionic neuron

rest and digest

set of functions associated with the parasympathetic system that lead to restful actions and digestion

sympathetic chain ganglia

series of ganglia adjacent to the vertebral column that receive input from central sympathetic neurons

sympathetic division

division of the autonomic nervous system associated with the fight-or-flight response

target effector

organ, tissue, or gland that will respond to the control of an autonomic or somatic or endocrine signal

terminal ganglia

ganglia of the parasympathetic division of the autonomic system, which are located near or within the target effector, the latter also known as intramural ganglia

thoracolumbar system

alternate name for the sympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in the lateral horn of the thoracic and upper lumbar spinal cord

varicosity

structure of some autonomic connections that is not a typical synaptic end bulb, but a string of swellings along the length of a fiber that makes a network of connections with the target effector

OU Human Physiology: Autonomic Reflexes and Homeostasis By the end of this section, you will be able to:

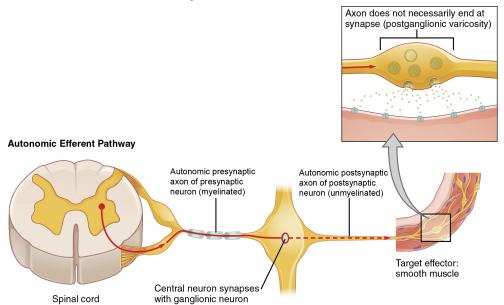
- Describe the players and their role in a reflex arc
- Explain the purpose of a visceral reflex
- Differentiate between short and long reflexes
- Determine the effect of the autonomic nervous system on the regulation of the various organ systems on the basis of the signaling molecules involved
- Explain the pupillary reflex in terms of ANS division, iris muscle contraction and pupil response
- Explain autonomic tone
- Describe the effects of drugs that affect autonomic function

Homeostasis is a dynamic balance between both the parasympathetic and sympathetic divisions of the autonomic nervous system. Close contact with the lioness will generate a sympathetic response which increases energy demands on the tissues and these demands must be met even, if other operations, such as digestion are temporarily suspended. In this situation, the activity of the sympathetic division increases and parasympathetic decreases. Once this contact with the lioness is over, the activity of the parasympathetic division will increase and activity of the sympathetic division will decrease. So how does the brain regulate the activities of these two divisions in effectors to maintain homeostasis? These changes are regulated via visceral reflexes.

The Structure of Visceral Reflex

The visceral reflex is divided into two parts, the **efferent branch** and the **afferent branch**. The efferent branch of the visceral reflex is a two-step pathway starting with the preganglionic fiber emerging from a lateral horn neuron in the spinal cord, or a cranial nucleus neuron in the brain stem, to a ganglion—followed by the postganglionic fiber projecting to a target effector. The other part of a reflex, the afferent branch, includes sensory neurons receiving input from the periphery—with cell bodies in the sensory ganglia, either of a cranial nerve or a dorsal root ganglion adjacent to the spinal cord that project into the CNS to initiate the reflex ([link]).

Visceral Reflex Pathway



Visceral reflexes involve a projection from the central neuron to a ganglion, followed by a second projection from the ganglion to the target effector.

Afferent Branch

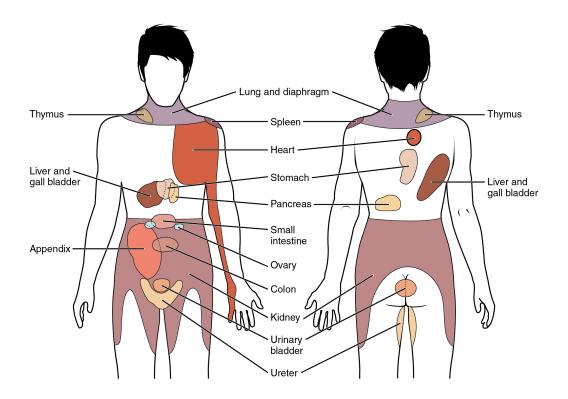
Many of the inputs to visceral reflexes are from special or somatic senses, but particular senses are associated with the viscera that are not part of the conscious perception of the environment. For example, there is a specific type of mechanoreceptor, called a **baroreceptor**, in the walls of the aorta and carotid sinuses that senses the stretch of those organs when blood volume or pressure increases. You do not have a conscious perception of having high blood pressure, but that is an important afferent branch of the cardiovascular and, particularly, vasomotor reflexes. The sensory neuron is essentially the same as any other general sensory neuron. The baroreceptor apparatus is part of the ending of a unipolar neuron that has a cell body in a sensory ganglion. The baroreceptors from the carotid arteries have axons in

the glossopharyngeal nerve, and those from the aorta have axons in the vagus nerve.

Though visceral senses are not primarily a part of conscious perception, those sensations sometimes make it to conscious awareness. If a visceral sense is strong enough, it will be perceived. The sensory homunculus—the representation of the body in the primary somatosensory cortex—only has a small region allotted for the perception of internal stimuli. If you swallow a large bolus of food, for instance, you will probably feel the lump of that food as it pushes through your esophagus, or even if your stomach is distended after a large meal. If you inhale especially cold air, you can feel it as it enters your larynx and trachea. These sensations are not the same as feeling high blood pressure or blood sugar levels.

When particularly strong visceral sensations rise to the level of conscious perception, the sensations are often felt in unexpected places. For example, strong visceral sensations of the heart will be felt as pain in the left shoulder and left arm. This irregular pattern of projection of conscious perception of visceral sensations is called **referred pain**. Depending on the organ system affected, the referred pain will project to different areas of the body ([link]). The location of referred pain is not random, but a definitive explanation of the mechanism has not been established. The most broadly accepted theory for this phenomenon is that the visceral sensory fibers enter into the same level of the spinal cord as the somatosensory fibers of the referred pain location. By this explanation, the visceral sensory fibers from the mediastinal region, where the heart is located, would enter the spinal cord at the same level as the spinal nerves from the shoulder and arm, so the brain misinterprets the sensations from the mediastinal region as being from the axillary and brachial regions. Projections from the medial and inferior divisions of the cervical ganglia do enter the spinal cord at the middle to lower cervical levels, which is where the somatosensory fibers enter.

Referred Pain Chart



Conscious perception of visceral sensations map to specific regions of the body, as shown in this chart. Some sensations are felt locally, whereas others are perceived as affecting areas that are quite distant from the involved organ.

Note:

Disorders of the...

Nervous System: Kehr's Sign

Kehr's sign is the presentation of pain in the left shoulder, chest, and neck regions following rupture of the spleen. The spleen is in the upper-left abdominopelvic quadrant, but the pain is more in the shoulder and neck. How can this be? The sympathetic fibers connected to the spleen are from the celiac ganglion, which would be from the mid-thoracic to lower thoracic region whereas parasympathetic fibers are found in the vagus nerve, which connects in the medulla of the brain stem. However, the neck and shoulder would connect to the spinal cord at the mid-cervical level of

the spinal cord. These connections do not fit with the expected correspondence of visceral and somatosensory fibers entering at the same level of the spinal cord.

The incorrect assumption would be that the visceral sensations are coming from the spleen directly. In fact, the visceral fibers are coming from the diaphragm. The nerve connecting to the diaphragm takes a special route. The phrenic nerve is connected to the spinal cord at cervical levels 3 to 5. The motor fibers that make up this nerve are responsible for the muscle contractions that drive ventilation. These fibers have left the spinal cord to enter the phrenic nerve, meaning that spinal cord damage below the midcervical level is not fatal by making ventilation impossible. Therefore, the visceral fibers from the diaphragm enter the spinal cord at the same level as the somatosensory fibers from the neck and shoulder.

The diaphragm plays a role in Kehr's sign because the spleen is just inferior to the diaphragm in the upper-left quadrant of the abdominopelvic cavity. When the spleen ruptures, blood spills into this region. The accumulating hemorrhage then puts pressure on the diaphragm. The visceral sensation is actually in the diaphragm, so the referred pain is in a region of the body that corresponds to the diaphragm, not the spleen.

Efferent Branch

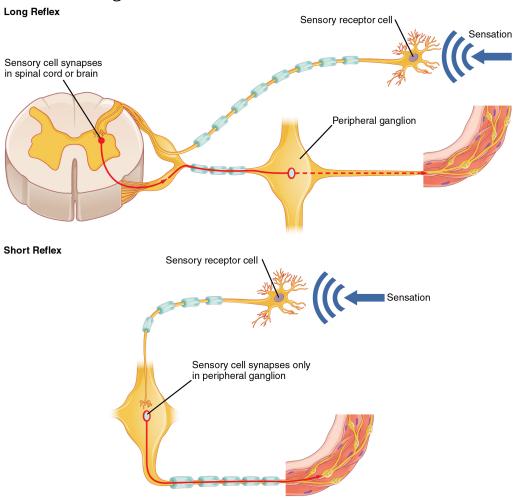
The efferent branch of the visceral reflex arc begins with the projection from the central neuron along the preganglionic fiber. This fiber then makes a synapse on the ganglionic neuron that projects to the target effector.

The effector organs that are the targets of the autonomic system range from the iris and ciliary body of the eye to the urinary bladder and reproductive organs. The thoracolumbar output, through the various sympathetic ganglia, reaches all of these organs. The cranial component of the parasympathetic system projects from the eye to part of the intestines. The sacral component picks up with the majority of the large intestine and the pelvic organs of the urinary and reproductive systems.

Short and Long Reflexes

Visceral reflexes that involve the thoracolumbar or craniosacral systems involve sensory neurons that connect sensory receptors to the central nervous system and efferent neurons that project to autonomic nervous system effectors. However, there are reflexes that do not need to involve any CNS components. A **long reflex** has afferent branches that enter the spinal cord or brain and involve the efferent branches, as previously explained. A **short reflex** is completely peripheral and only involves the local integration of sensory input with motor output ([link]).

Short and Long Reflexes



Sensory input can stimulate either a short or a long reflex.
A sensory neuron can project to the CNS or to an autonomic ganglion. The short reflex involves the direct

stimulation of a postganglionic fiber by the sensory neuron, whereas the long reflex involves integration in the spinal cord or brain.

The difference between short and long reflexes is in the involvement of the CNS. In the autonomic system there is the possibility that the CNS is not involved. Because the efferent branch of a visceral reflex involves two neurons—the central neuron and the ganglionic neuron—a "short circuit" can be possible. If a sensory neuron projects directly to the ganglionic neuron and causes it to activate the effector target, then the CNS is not involved.

A division of the nervous system that is related to the autonomic nervous system is the enteric nervous system. The word enteric refers to the digestive organs, so this represents the nervous tissue that is part of the digestive system. There are a few myenteric plexuses in which the nervous tissue in the wall of the digestive tract organs can directly influence digestive function. If stretch receptors in the stomach are activated by the filling and distension of the stomach, a short reflex will directly activate the smooth muscle fibers of the stomach wall to increase motility to digest the excessive food in the stomach. No CNS involvement is needed because the stretch receptor is directly activating a neuron in the wall of the stomach that causes the smooth muscle to contract. That neuron, connected to the smooth muscle, is a postganglionic parasympathetic neuron that can be controlled by a fiber found in the vagus nerve.

Note:



Read this <u>article</u> to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?

Balance in Competing Autonomic Reflex Arcs

The autonomic nervous system is important for homeostasis because its two divisions compete at the target effector. The balance of homeostasis is attributable to the competing inputs from the sympathetic and parasympathetic divisions (dual innervation). At the level of the target effector, the signal of which system is sending the message is strictly chemical. A signaling molecule binds to a receptor that causes changes in the target cell, which in turn causes the tissue or organ to respond to the changing conditions of the body.

Competing Neurotransmitters

The postganglionic fibers of the sympathetic and parasympathetic divisions both release neurotransmitters that bind to receptors on their targets. Postganglionic sympathetic fibers release norepinephrine, with a minor exception, whereas postganglionic parasympathetic fibers release ACh. For any given target, the difference in which division of the autonomic nervous system is exerting control is just in what chemical binds to its receptors. The target cells will have adrenergic and muscarinic receptors. If norepinephrine is released, it will bind to the adrenergic receptors present on the target cell, and if ACh is released, it will bind to the muscarinic receptors on the target cell.

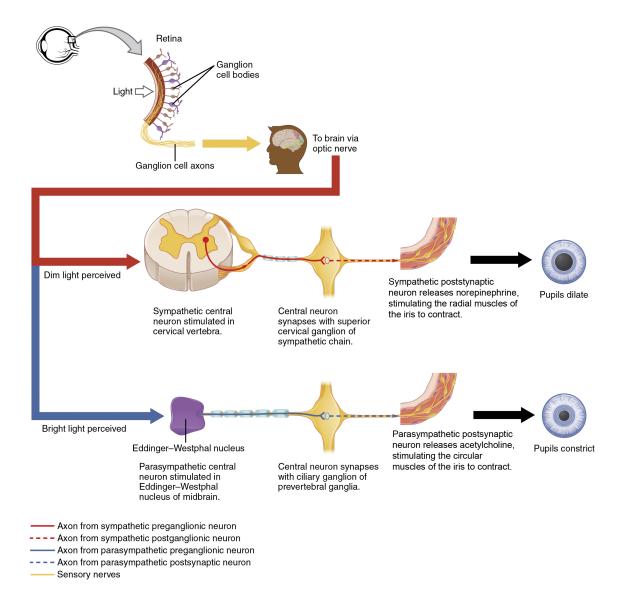
In the sympathetic system, there are exceptions to this pattern of dual innervation. The postganglionic sympathetic fibers that contact the blood vessels within skeletal muscle and that contact sweat glands do not release

norepinephrine, they release ACh. This does not create any problem because there is no parasympathetic input to the sweat glands. Sweat glands have muscarinic receptors and produce and secrete sweat in response to the presence of ACh.

At most of the other targets of the autonomic system, the effector response is based on which neurotransmitter is released and what receptor is present. For example, regions of the heart that establish heart rate are contacted by postganglionic fibers from both systems. If norepinephrine is released onto those cells, it binds to an adrenergic receptor that causes the cells to depolarize faster, and the heart rate increases. If ACh is released onto those cells, it binds to a muscarinic receptor that causes the cells to hyperpolarize so that they cannot reach threshold as easily, and the heart rate slows. Without this parasympathetic input, the heart would work at a rate of approximately 100 beats per minute (bpm). The sympathetic system speeds that up, as it would during exercise, to 120–140 bpm, for example. The parasympathetic system slows it down to the resting heart rate of 60–80 bpm.

Another example is in the control of pupillary size ([link]). The afferent branch responds to light hitting the retina. Photoreceptors are activated, and the signal is transferred to the retinal ganglion cells that send an action potential along the optic nerve into the diencephalon. If light levels are low, the sympathetic system sends a signal out through the upper thoracic spinal cord to the superior cervical ganglion of the sympathetic chain. The postganglionic fiber then projects to the iris, where it releases norepinephrine onto the radial fibers of the iris (a smooth muscle). When those fibers contract, the pupil dilates—increasing the amount of light hitting the retina. If light levels are too high, the parasympathetic system sends a signal out from the Eddinger–Westphal nucleus through the oculomotor nerve. This fiber synapses in the ciliary ganglion in the posterior orbit. The postganglionic fiber then projects to the iris, where it releases ACh onto the circular fibers of the iris—another smooth muscle. When those fibers contract, the pupil constricts to limit the amount of light hitting the retina.

Autonomic Control of Pupillary Size



Activation of the pupillary reflex comes from the amount of light activating the retinal ganglion cells, as sent along the optic nerve. The output of the sympathetic system projects through the superior cervical ganglion, whereas the parasympathetic system originates out of the midbrain and projects through the oculomotor nerve to the ciliary ganglion, which then projects to the iris. The postganglionic fibers of either division release neurotransmitters onto the smooth muscles of the iris to cause changes in the pupillary size. Norepinephrine results in dilation and ACh results in constriction.

In this example, the autonomic system is controlling how much light hits the retina. It is a homeostatic reflex mechanism that keeps the activation of photoreceptors within certain limits. In the context of avoiding a threat like the lioness on the savannah, the sympathetic response for fight or flight will increase pupillary diameter so that more light hits the retina and more visual information is available for running away. Likewise, the parasympathetic response of rest reduces the amount of light reaching the retina via pupillary constriction.

Note:



Watch this <u>video</u> to learn about the pupillary reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and efferent branches of the competing reflex (dilation)?

Autonomic Tone

Organ systems are balanced between the input from the sympathetic and parasympathetic divisions. When something upsets that balance, the homeostatic mechanisms strive to return it to its regular state. For each organ system, there may be more of a sympathetic or parasympathetic tendency to the resting state, which is known as the **autonomic tone** of the system. For example, the heart rate was described above. Because the

resting heart rate is the result of the parasympathetic system slowing the heart down from its intrinsic rate of 100 bpm, the heart can be said to be in parasympathetic tone.

In a similar fashion, another aspect of the cardiovascular system is primarily under sympathetic control. Blood pressure is partially determined by the contraction of smooth muscle in the walls of blood vessels. These tissues have adrenergic receptors that respond to the release of norepinephrine from postganglionic sympathetic fibers by constricting and increasing blood pressure. The hormones released from the adrenal medulla —epinephrine and norepinephrine—will also bind to these receptors. Those hormones travel through the bloodstream where they can easily interact with the receptors in the vessel walls. The parasympathetic system has no significant input to the systemic blood vessels, so the sympathetic system determines their tone.

There are a limited number of blood vessels that respond to sympathetic input in a different fashion. Blood vessels in skeletal muscle, particularly those in the lower limbs, are more likely to dilate. It does not have an overall effect on blood pressure to alter the tone of the vessels, but rather allows for blood flow to increase for those skeletal muscles that will be active in the fight-or-flight response. The blood vessels that have a parasympathetic projection are limited to those in the erectile tissue of the reproductive organs. Acetylcholine released by these postganglionic parasympathetic fibers cause the vessels to dilate, leading to the engorgement of the erectile tissue.

Note:

Homeostatic Imbalances Orthostatic Hypotension

Have you ever stood up quickly and felt dizzy for a moment? This is because, for one reason or another, blood is not getting to your brain so it is briefly deprived of oxygen. When you change position from sitting or lying down to standing, your cardiovascular system has to adjust for a new challenge, keeping blood pumping up into the head while gravity is pulling more and more blood down into the legs.

The reason for this is a sympathetic reflex that maintains the output of the heart in response to postural change. When a person stands up, proprioceptors indicate that the body is changing position. A signal goes to the CNS, which then sends a signal to the upper thoracic spinal cord neurons of the sympathetic division. The sympathetic system then causes the heart to beat faster and the blood vessels to constrict. Both changes will make it possible for the cardiovascular system to maintain the rate of blood delivery to the brain. Blood is being pumped superiorly through the internal branch of the carotid arteries into the brain, against the force of gravity. Gravity is not increasing while standing, but blood is more likely to flow down into the legs as they are extended for standing. This sympathetic reflex keeps the brain well oxygenated so that cognitive and other neural processes are not interrupted.

Sometimes this does not work properly. If the sympathetic system cannot increase cardiac output, then blood pressure into the brain will decrease, and a brief neurological loss can be felt. This can be brief, as a slight "wooziness" when standing up too quickly, or a loss of balance and neurological impairment for a period of time. The name for this is orthostatic hypotension, which means that blood pressure goes below the homeostatic set point when standing. It can be the result of standing up faster than the reflex can occur, which may be referred to as a benign "head rush," or it may be the result of an underlying cause.

There are two basic reasons that orthostatic hypotension can occur. First, blood volume is too low and the sympathetic reflex is not effective. This hypovolemia may be the result of dehydration or medications that affect fluid balance, such as diuretics or vasodilators. Both of these medications are meant to lower blood pressure, which may be necessary in the case of systemic hypertension, and regulation of the medications may alleviate the problem. Sometimes increasing fluid intake or water retention through salt intake can improve the situation.

The second underlying cause of orthostatic hypotension is autonomic failure. There are several disorders that result in compromised sympathetic functions. The disorders range from diabetes to multiple system atrophy (a loss of control over many systems in the body), and addressing the underlying condition can improve the hypotension. For example, with diabetes, peripheral nerve damage can occur, which would affect the

postganglionic sympathetic fibers. Getting blood glucose levels under control can improve neurological deficits associated with diabetes.

Chapter Review

Autonomic nervous system function is based on the visceral reflex. This reflex is similar to the somatic reflex, but the efferent branch is composed of two neurons. The central neuron projects from the spinal cord or brain stem to synapse on the postganglionic neuron that projects to the effector. The afferent branch of the somatic and visceral reflexes is very similar, as many somatic and special senses activate autonomic responses. However, there are visceral senses that do not form part of conscious perception. If a visceral sensation, such as cardiac pain, is strong enough, it will rise to the level of consciousness. However, the sensory homunculus does not provide a representation of the internal structures to the same degree as the surface of the body, so visceral sensations are often experienced as referred pain, such as feelings of pain in the left shoulder and arm in connection with a heart attack.

The role of visceral reflexes is to maintain a balance of function in the organ systems of the body. The two divisions of the autonomic system each play a role in effecting change, usually in competing directions. The sympathetic system increases heart rate, whereas the parasympathetic system decreases heart rate. The sympathetic system dilates the pupil of the eye, whereas the parasympathetic system constricts the pupil. The competing inputs can contribute to the resting tone of the organ system. Heart rate is normally under parasympathetic tone, whereas blood pressure is normally under sympathetic tone. The heart rate is slowed by the autonomic system at rest, whereas blood vessels retain a slight constriction at rest.

In a few systems of the body, the competing input from the two divisions is not the norm. The sympathetic tone of blood vessels is caused by the lack of parasympathetic input to the systemic circulatory system. Only certain regions receive parasympathetic input that relaxes the smooth muscle wall

of the blood vessels. Sweat glands are another example, which only receive input from the sympathetic system.

Glossary

afferent branch

component of a reflex arc that represents the input from a sensory neuron, for either a special or general sense

autonomic tone

tendency of an organ system to be governed by one division of the autonomic nervous system over the other, such as heart rate being lowered by parasympathetic input at rest

baroreceptor

mechanoreceptor that senses the stretch of blood vessels to indicate changes in blood pressure

efferent branch

component of a reflex arc that represents the output, with the target being an effector, such as muscle or glandular tissue

long reflex

reflex arc that includes the central nervous system

short reflex

reflex arc that does not include any components of the central nervous system

visceral reflex

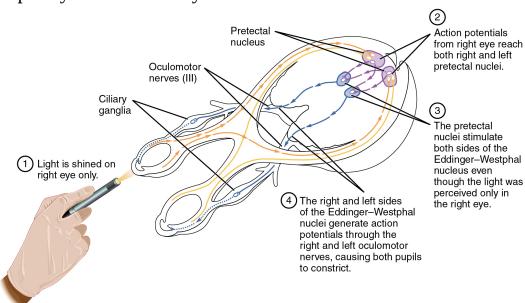
reflex involving an internal organ as the effector, under the control of the autonomic nervous system

OU Human Physiology: Central Control By the end of this section, you will be able to:

- Explain the role of the hypothalamus in homeostasis
- Explain the role of the amygdala
- List the three centers in the medulla and their importance

The pupillary light reflex ([link]) begins when light hits the retina and causes a signal to travel along the optic nerve. This is visual sensation, because the afferent branch of this reflex is simply sharing the special sense pathway. Bright light hitting the retina leads to the parasympathetic response, through the oculomotor nerve, followed by the postganglionic fiber from the ciliary ganglion, which stimulates the circular fibers of the iris to contract and constrict the pupil. When light hits the retina in one eye, both pupils contract. When that light is removed, both pupils dilate again back to the resting position. When the stimulus is unilateral (presented to only one eye), the response is bilateral (both eyes). If you touch a hot radiator, you only pull that arm back, not both. The hypothalamus, along with other CNS locations, controls the autonomic system.

Pupillary Reflex Pathways



The pupil is under competing autonomic control in response to light levels hitting the retina. The sympathetic system will dilate the pupil when the retina is not receiving enough light, and the parasympathetic system will constrict the pupil when too much light hits the retina.

Forebrain Structures

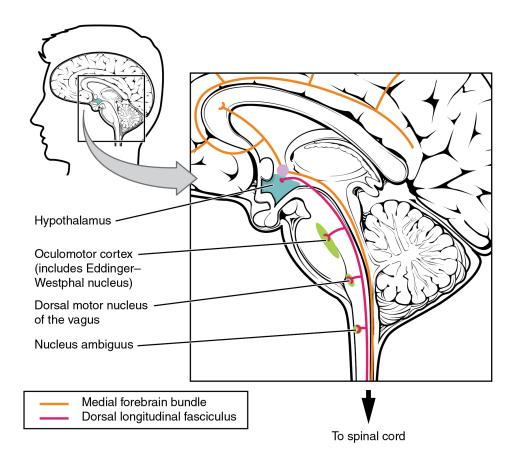
Autonomic control is based on the visceral reflexes, composed of the afferent and efferent branches. These homeostatic mechanisms are based on the balance between the two divisions of the autonomic system, which results in tone for various organs that is based on the predominant input from the sympathetic or parasympathetic systems. Coordinating that balance requires integration that begins with forebrain structures like the hypothalamus and continues into the brain stem and spinal cord.

The Hypothalamus

The hypothalamus is the control center for many homeostatic mechanisms. It regulates both autonomic function and endocrine function. The roles it plays in the pupillary reflexes demonstrates the importance of this control center. The optic nerve projects primarily to the thalamus, which is the necessary relay to the occipital cortex for conscious visual perception. Another projection of the optic nerve, however, goes to the hypothalamus.

The hypothalamus then uses this visual system input to drive the pupillary reflexes. If the retina is activated by high levels of light, the hypothalamus stimulates the parasympathetic response. If the optic nerve message shows that low levels of light are falling on the retina, the hypothalamus activates the sympathetic response. Output from the hypothalamus follows two main tracts, the **dorsal longitudinal fasciculus** and the **medial forebrain bundle** ([link]). Along these two tracts, the hypothalamus can influence the Eddinger–Westphal nucleus of the oculomotor complex or the lateral horns of the thoracic spinal cord.

Fiber Tracts of the Central Autonomic System



The hypothalamus is the source of most of the central control of autonomic function. It receives input from cerebral structures and projects to brain stem and spinal cord structures to regulate the balance of sympathetic and parasympathetic input to the organ systems of the body. The main pathways for this are the medial forebrain bundle and the dorsal longitudinal fasciculus.

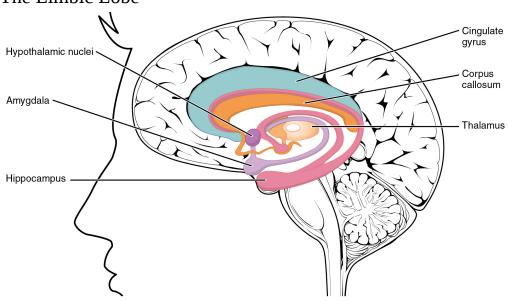
These two tracts connect the hypothalamus with the major parasympathetic nuclei in the brain stem and the preganglionic (central) neurons of the thoracolumbar spinal cord. The hypothalamus also receives input from other areas of the forebrain through the medial forebrain bundle. The olfactory cortex, the septal nuclei of the basal forebrain, and the amygdala project into the hypothalamus through the medial forebrain bundle. These

forebrain structures inform the hypothalamus about the state of the nervous system and can influence the regulatory processes of homeostasis. A good example of this is found in the amygdala, which is found beneath the cerebral cortex of the temporal lobe and plays a role in our ability to remember and feel emotions.

The Amygdala

The amygdala is a group of nuclei in the medial region of the temporal lobe that is part of the **limbic lobe** ([link]). The limbic lobe includes structures that are involved in emotional responses, as well as structures that contribute to memory function. The limbic lobe has strong connections with the hypothalamus and influences the state of its activity on the basis of emotional state. For example, when you are anxious or scared, the amygdala will send signals to the hypothalamus along the medial forebrain bundle that will stimulate the sympathetic fight-or-flight response. The hypothalamus will also stimulate the release of stress hormones through its control of the endocrine system in response to amygdala input.

The Limbic Lobe



Structures arranged around the edge of the cerebrum constitute the limbic lobe, which includes the amygdala,

hippocampus, and cingulate gyrus, and connects to the hypothalamus.

The Medulla

The medulla contains nuclei referred to as the **cardiovascular center**, which controls the smooth and cardiac muscle of the cardiovascular system through autonomic connections. When the homeostasis of the cardiovascular system shifts, such as when blood pressure changes, the coordination of the autonomic system can be accomplished within this region. Furthermore, when descending inputs from the hypothalamus stimulate this area, the sympathetic system can increase activity in the cardiovascular system, such as in response to anxiety or stress. The preganglionic sympathetic fibers that are responsible for increasing heart rate are referred to as the **cardiac accelerator nerves**, whereas the preganglionic sympathetic fibers responsible for constricting blood vessels compose the **vasomotor nerves**.

Several brain stem nuclei are important for the visceral control of major organ systems. One brain stem nucleus involved in cardiovascular function is the solitary nucleus. It receives sensory input about blood pressure and cardiac function from the glossopharyngeal and vagus nerves, and its output will activate sympathetic stimulation of the heart or blood vessels through the upper thoracic lateral horn. Another brain stem nucleus important for visceral control is the dorsal motor nucleus of the vagus nerve, which is the motor nucleus for the parasympathetic functions ascribed to the vagus nerve, including decreasing the heart rate, relaxing bronchial tubes in the lungs, and activating digestive function through the enteric nervous system. The nucleus ambiguus, which is named for its ambiguous histology, also contributes to the parasympathetic output of the vagus nerve and targets muscles in the pharynx and larynx for swallowing and speech, as well as contributing to the parasympathetic tone of the heart along with the dorsal motor nucleus of the vagus.

The medulla also contains the respiratory center which controls breathing rate and the digestive tract. Both of which are also important to maintaining

homeostasis.

Note:

Everyday Connections

Exercise and the Autonomic System

In addition to its association with the fight-or-flight response and rest-and-digest functions, the autonomic system is responsible for certain everyday functions. For example, it comes into play when homeostatic mechanisms dynamically change, such as the physiological changes that accompany exercise. Getting on the treadmill and putting in a good workout will cause the heart rate to increase, breathing to be stronger and deeper, sweat glands to activate, and the digestive system to suspend activity. These are the same physiological changes associated with the fight-or-flight response, but there is nothing chasing you on that treadmill.

This is not a simple homeostatic mechanism at work because "maintaining the internal environment" would mean getting all those changes back to their set points. Instead, the sympathetic system has become active during exercise so that your body can cope with what is happening. A homeostatic mechanism is dealing with the conscious decision to push the body away from a resting state. The heart, actually, is moving away from its homeostatic set point. Without any input from the autonomic system, the heart would beat at approximately 100 bpm, and the parasympathetic system slows that down to the resting rate of approximately 70 bpm. But in the middle of a good workout, you should see your heart rate at 120–140 bpm. You could say that the body is stressed because of what you are doing to it. Homeostatic mechanisms are trying to keep blood pH in the normal range, or to keep body temperature under control, but those are in response to the choice to exercise.

Note:			



Watch this <u>video</u> to learn about physical responses to emotion. The autonomic system, which is important for regulating the homeostasis of the organ systems, is also responsible for our physiological responses to emotions such as fear. The video summarizes the extent of the body's reactions and describes several effects of the autonomic system in response to fear. On the basis of what you have already studied about autonomic function, which effect would you expect to be associated with parasympathetic, rather than sympathetic, activity?

Chapter Review

The autonomic system integrates sensory information and higher cognitive processes to generate output, which balances homeostatic mechanisms. The central autonomic structure is the hypothalamus, which coordinates sympathetic and parasympathetic efferent pathways to regulate activities of the organ systems of the body. The majority of hypothalamic output travels through the medial forebrain bundle and the dorsal longitudinal fasciculus to influence brain stem and spinal components of the autonomic nervous system. The medial forebrain bundle also connects the hypothalamus with higher centers of the limbic system where emotion can influence visceral responses. The amygdala is a structure within the limbic system that influences the hypothalamus in the regulation of the autonomic system, as well as the endocrine system.

These higher centers have descending control of the autonomic system through brain stem centers, primarily in the medulla, such as the cardiovascular center. This collection of medullary nuclei regulates cardiac function, as well as blood pressure. Sensory input from the heart, aorta, and carotid sinuses project to these regions of the medulla. The solitary nucleus

increases sympathetic tone of the cardiovascular system through the cardiac accelerator and vasomotor nerves. The nucleus ambiguus and the dorsal motor nucleus both contribute fibers to the vagus nerve, which exerts parasympathetic control of the heart by decreasing heart rate.

Glossary

cardiac accelerator nerves

preganglionic sympathetic fibers that cause the heart rate to increase when the cardiovascular center in the medulla initiates a signal

cardiovascular center

region in the medulla that controls the cardiovascular system through cardiac accelerator nerves and vasomotor nerves, which are components of the sympathetic division of the autonomic nervous system

dorsal longitudinal fasciculus

major output pathway of the hypothalamus that descends through the gray matter of the brain stem and into the spinal cord

limbic lobe

structures arranged around the edges of the cerebrum that are involved in memory and emotion

medial forebrain bundle

fiber pathway that extends anteriorly into the basal forebrain, passes through the hypothalamus, and extends into the brain stem and spinal cord

vasomotor nerves

preganglionic sympathetic fibers that cause the constriction of blood vessels in response to signals from the cardiovascular center

OU Human Physiology: Drugs that Affect the Autonomic System By the end of this section, you will be able to:

- List the classes of pharmaceuticals that interact with the autonomic nervous system
- Differentiate between cholinergic and adrenergic compounds
- Differentiate between sympathomimetic and sympatholytic drugs
- Relate the consequences of nicotine abuse with respect to autonomic control of the cardiovascular system

An important way to understand the effects of native neurochemicals in the autonomic system is in considering the effects of pharmaceutical drugs. This can be considered in terms of how drugs change autonomic function. These effects will primarily be based on how drugs act at the receptors of the autonomic system neurochemistry. The signaling molecules of the nervous system interact with proteins in the cell membranes of various target cells. In fact, no effect can be attributed to just the signaling molecules themselves without considering the receptors. A chemical that the body produces to interact with those receptors is called an **endogenous chemical**, whereas a chemical introduced to the system from outside is an **exogenous chemical**. Exogenous chemicals may be of a natural origin, such as a plant extract, or they may be synthetically produced in a pharmaceutical laboratory.

Broad Autonomic Effects

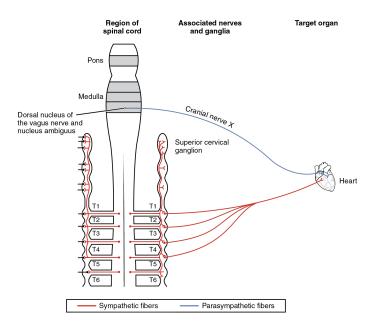
One important drug that affects the autonomic system broadly is not a pharmaceutical therapeutic agent associated with the system. This drug is nicotine. The effects of nicotine on the autonomic nervous system are important in considering the role smoking can play in health.

All ganglionic neurons of the autonomic system, in both sympathetic and parasympathetic ganglia, are activated by ACh released from preganglionic fibers. The ACh receptors on these neurons are of the nicotinic type, meaning that they are ligand-gated ion channels. When the neurotransmitter released from the preganglionic fiber binds to the receptor protein, a channel opens to allow positive ions to cross the cell membrane. The result is depolarization of the ganglia. Nicotine acts as an ACh analog at these synapses, so when someone takes in the drug, it binds to these ACh receptors and activates the ganglionic neurons, causing them to depolarize.

Ganglia of both divisions are activated equally by the drug. For many target organs in the body, this results in no net change. The competing inputs to the system cancel each other out and nothing significant happens. For example, the sympathetic system will cause sphincters in the digestive tract to contract, limiting digestive propulsion, but the parasympathetic system will cause the contraction of other muscles in the digestive tract, which will try to push the contents of the digestive system along. The end result is that the food does not really move along and the digestive system has not appreciably changed.

The system in which this can be problematic is in the cardiovascular system, which is why smoking is a risk factor for cardiovascular disease. First, there is no significant parasympathetic regulation of blood pressure. Only a limited number of blood vessels are affected by parasympathetic input, so nicotine will preferentially cause the vascular tone to become more sympathetic, which means blood pressure will be increased. Second, the autonomic control of the heart is special. Unlike skeletal or smooth muscles, cardiac muscle is intrinsically active, meaning that it generates its own action potentials. The autonomic system does not cause the heart to beat, it just speeds it up (sympathetic) or slows it down (parasympathetic). The mechanisms for this are not mutually exclusive, so the heart receives conflicting signals, and the rhythm of the heart can be affected ([link]).

Autonomic Connections to Heart and Blood Vessels



The nicotinic receptor is found on all autonomic ganglia, but the cardiovascular connections are particular, and do not conform to the usual competitive projections that would just cancel each other out when stimulated by nicotine. The opposing signals to the heart would both depolarize and hyperpolarize the heart cells that establish the rhythm of the heartbeat, likely causing arrhythmia. Only the sympathetic system governs systemic blood pressure so nicotine would cause an increase.

Sympathetic Effect

The neurochemistry of the sympathetic system is based on the adrenergic system. Norepinephrine and epinephrine influence target effectors by binding to the α -adrenergic or β -adrenergic receptors. Drugs that affect the sympathetic system affect these chemical systems. The drugs can be classified by whether they enhance the functions of the sympathetic system or interrupt those functions. A drug that enhances adrenergic function is known as a **sympathomimetic drug**, whereas a drug that interrupts adrenergic function is a **sympatholytic drug**.

Sympathomimetic Drugs

When the sympathetic system is not functioning correctly or the body is in a state of homeostatic imbalance, these drugs act at postganglionic terminals and synapses in the sympathetic efferent pathway. These drugs either bind to particular adrenergic receptors and mimic norepinephrine at the synapses between sympathetic postganglionic fibers and their targets, or they increase the production and release of norepinephrine from postganglionic fibers. Also, to increase the effectiveness of adrenergic chemicals released from the fibers, some of these drugs may block the removal or reuptake of the neurotransmitter from the synapse.

A common sympathomimetic drug is phenylephrine, which is a common component of decongestants. It can also be used to dilate the pupil and to raise blood pressure. Phenylephrine is known as an α_1 -adrenergic **agonist**, meaning that it binds to a specific adrenergic receptor, stimulating a response. In this role, phenylephrine will bind to the adrenergic receptors in bronchioles of the lungs and cause them to dilate. By opening these structures,

accumulated mucus can be cleared out of the lower respiratory tract. Phenylephrine is often paired with other pharmaceuticals, such as analgesics, as in the "sinus" version of many over-the-counter drugs, such as Tylenol Sinus[®] or Excedrin Sinus[®], or in expectorants for chest congestion such as in Robitussin CF[®].

A related molecule, called pseudoephedrine, was much more commonly used in these applications than was phenylephrine, until the molecule became useful in the illicit production of amphetamines. Phenylephrine is not as effective as a drug because it can be partially broken down in the digestive tract before it is ever absorbed. Like the adrenergic agents, phenylephrine is effective in dilating the pupil, known as **mydriasis** ([link]). Phenylephrine is used during an eye exam in an ophthalmologist's or optometrist's office for this purpose. It can also be used to increase blood pressure in situations in which cardiac function is compromised, such as under anesthesia or during septic shock.

Mydriasis



The sympathetic system causes pupillary dilation when norepinephrine binds to an adrenergic receptor in the radial fibers of the iris smooth muscle. Phenylephrine mimics this action by binding to the same receptor when drops are applied onto the surface of the eye in a doctor's office. (credit: Corey Theiss)

Other drugs that enhance adrenergic function are not associated with therapeutic uses, but affect the functions of the sympathetic system in a similar fashion. Cocaine primarily interferes with the uptake of dopamine at the synapse and can also increase adrenergic function. Caffeine is an antagonist to a different neurotransmitter receptor, called the adenosine receptor. Adenosine will suppress adrenergic activity, specifically the release of norepinephrine at synapses, so caffeine indirectly increases adrenergic activity. There is some evidence that caffeine can aid in the therapeutic use of drugs, perhaps by potentiating (increasing) sympathetic function, as is suggested by the inclusion of caffeine in over-the-counter analgesics such as Excedrin[®].

Sympatholytic Drugs

Drugs that interfere with sympathetic function are referred to as sympatholytic, or sympathoplegic, drugs. They primarily work as an **antagonist** to the adrenergic receptors. They block the ability of norepinephrine or epinephrine to bind to the receptors so that the effect is "cut" or "takes a blow," to refer to the endings "-lytic" and "-plegic," respectively. The various drugs of this class will be specific to α -adrenergic or β -adrenergic receptors, or to their receptor subtypes.

Possibly the most familiar type of sympatholytic drug are the β -blockers. These drugs are often used to treat cardiovascular disease because they block the β -receptors associated with vasoconstriction and cardioacceleration.

By allowing blood vessels to dilate, or keeping heart rate from increasing, these drugs can improve cardiac function in a compromised system, such as for a person with congestive heart failure or who has previously suffered a heart attack. A couple of common versions of β -blockers are metaprolol, which specifically blocks the β_2 -receptor, and propanolol, which nonspecifically blocks β -receptors. There are other drugs that are α -blockers and can affect the sympathetic system in a similar way.

Other uses for sympatholytic drugs are as antianxiety medications. A common example of this is clonidine, which is an α -blocker. The sympathetic system is tied to anxiety to the point that the sympathetic response can be referred to as "fight, flight, or fright." Clonidine is used for other treatments aside from hypertension and anxiety, including pain conditions and attention deficit hyperactivity disorder.

Parasympathetic Effects

Drugs affecting parasympathetic functions can be classified into those that increase or decrease activity at postganglionic terminals. Parasympathetic postganglionic fibers release ACh, and the receptors on the targets are muscarinic receptors. There are several types of muscarinic receptors, M1–M5, but the drugs are not usually specific to the specific types. Parasympathetic drugs can be either muscarinic agonists or antagonists, or have indirect effects on the cholinergic system. Drugs that enhance cholinergic effects are called **parasympathomimetic drugs**, whereas those that inhibit cholinergic effects are referred to as **anticholinergic drugs**.

Pilocarpine is a nonspecific muscarinic agonist commonly used to treat disorders of the eye. It reverses mydriasis, such as is caused by phenylephrine, and can be administered after an eye exam. Along with constricting the pupil through the smooth muscle of the iris, pilocarpine will also cause the ciliary muscle to contract. This will open perforations at the base of the cornea, allowing for the drainage of aqueous humor from the anterior compartment of the eye and, therefore, reducing intraocular pressure related to glaucoma.

Atropine and scopolamine are part of a class of muscarinic antagonists that come from the *Atropa* genus of plants that include belladonna or deadly nightshade ([link]). The name of one of these plants, belladonna, refers to the fact that extracts from this plant were used cosmetically for dilating the pupil. The active chemicals from this plant block the muscarinic receptors in the iris and allow the pupil to dilate, which is considered attractive because it makes the eyes appear larger. Humans are instinctively attracted to anything with larger eyes, which comes from the fact that the ratio of eye-to-head size is different in infants (or baby animals) and can elicit an emotional response. The cosmetic use of belladonna extract was essentially acting on this response. Atropine is no longer used in this cosmetic capacity for reasons related to the other name for the plant, which is deadly nightshade. Suppression of parasympathetic function, especially when it becomes systemic, can be fatal. Autonomic regulation is disrupted and anticholinergic symptoms develop. The berries of this plant are highly toxic, but can be mistaken for other berries. The antidote for atropine or scopolamine poisoning is pilocarpine.

Belladonna Plant



The plant from the genus *Atropa*, which is known as belladonna or deadly nightshade, was used cosmetically to dilate pupils, but can

be fatal when ingested. The berries on the plant may seem attractive as a fruit, but they contain the same anticholinergic compounds as the rest of the plant.

Drug type	Example(s)	Sympathetic effect	Parasympathetic effect	Overall resul
Nicotinic agonists	Nicotine	Mimic ACh at preganglionic synapses, causing activation of postganglionic fibers and the release of norepinephrine onto the target organ	Mimic ACh at preganglionic synapses, causing activation of postganglionic fibers and the release of ACh onto the target organ	Most conflicting signals cancel each other out but cardiovascular system is susceptible to hypertension and arrhythmi
Sympathomimetic drugs	Phenylephrine	Bind to adrenergic receptors or mimics sympathetic action in some other way	No effect	Increase sympathetic tone
Sympatholytic drugs	β-blockers such as propanolol or metaprolol; α- blockers such as clonidine	Block binding to adrenergic drug or decrease adrenergic signals	No effect	Increase parasympathe tone
Parasymphatho- mimetics/muscarinic agonists	Pilocarpine	No effect, except on sweat glands	Bind to muscarinic receptor, similar to ACh	Increase parasympathe tone
Anticholinergics/muscarinic antagonists	Atropine, scopolamine, dimenhydrinate	No effect	Block muscarinic receptors and parasympathetic function	Increase sympathetic tone

Note:

Disorders of the...

Autonomic Nervous System

Approximately 33 percent of people experience a mild problem with motion sickness, whereas up to 66 percent experience motion sickness under extreme conditions, such as being on a tossing boat with no view of the horizon. Connections between regions in the brain stem and the autonomic system result in the symptoms of nausea, cold sweats, and vomiting.

The part of the brain responsible for vomiting, or emesis, is known as the area postrema. It is located next to the fourth ventricle and is not restricted by the blood–brain barrier, which allows it to respond to chemicals in the bloodstream—namely, toxins that will stimulate emesis. There are significant connections between this area, the solitary nucleus, and the dorsal motor nucleus of the vagus nerve. These autonomic system and nuclei connections are associated with the symptoms of motion sickness.

Motion sickness is the result of conflicting information from the visual and vestibular systems. If motion is perceived by the visual system without the complementary vestibular stimuli, or through vestibular stimuli without visual confirmation, the brain stimulates emesis and the associated symptoms. The area postrema, by itself, appears to be able to stimulate emesis in response to toxins in the blood, but it is also connected to the autonomic system and can trigger a similar response to motion.

Autonomic drugs are used to combat motion sickness. Though it is often described as a dangerous and deadly drug, scopolamine is used to treat motion sickness. A popular treatment for motion sickness is the transdermal scopolamine patch. Scopolamine is one of the substances derived from the *Atropa* genus along with atropine. At higher doses, those substances are thought to be poisonous and can lead to an extreme sympathetic syndrome. However, the transdermal patch regulates the release of the drug, and the concentration is kept very low so that the dangers are avoided. For those who are concerned about using "The Most Dangerous Drug," as some websites will call it, antihistamines such as dimenhydrinate (Dramamine[®]) can be used.

Note:



Watch this <u>video</u> to learn about the side effects of 3-D movies. As discussed in this video, movies that are shot in 3-D can cause motion sickness, which elicits the autonomic symptoms of nausea and sweating. The disconnection between the perceived motion on the screen and the lack of any change in equilibrium stimulates these symptoms. Why do you think sitting close to the screen or right in the middle of the theater makes motion sickness during a 3-D movie worse?

Chapter Review

The autonomic system is affected by a number of exogenous agents, including some that are therapeutic and some that are illicit. These drugs affect the autonomic system by mimicking or interfering with the endogenous agents or their receptors. A survey of how different drugs affect autonomic function illustrates the role that the neurotransmitters and hormones play in autonomic function. Drugs can be thought of as chemical tools to effect changes in the system with some precision, based on where those drugs are effective.

Nicotine is not a drug that is used therapeutically, except for smoking cessation. When it is introduced into the body via products, it has broad effects on the autonomic system. Nicotine carries a risk for cardiovascular disease because of these broad effects. The drug stimulates both sympathetic and parasympathetic ganglia at the preganglionic fiber synapse. For most organ systems in the body, the competing input from the two postganglionic fibers will essentially cancel each other out. However, for the cardiovascular system, the results are different.

Because there is essentially no parasympathetic influence on blood pressure for the entire body, the sympathetic input is increased by nicotine, causing an increase in blood pressure. Also, the influence that the autonomic system has on the heart is not the same as for other systems. Other organs have smooth muscle or glandular tissue that is activated or inhibited by the autonomic system. Cardiac muscle is intrinsically active and is modulated by the autonomic system. The contradictory signals do not just cancel each other out, they alter the regularity of the heart rate and can cause arrhythmias. Both hypertension and arrhythmias are risk factors for heart disease.

Other drugs affect one division of the autonomic system or the other. The sympathetic system is affected by drugs that mimic the actions of adrenergic molecules (norepinephrine and epinephrine) and are called sympathomimetic drugs. Drugs such as phenylephrine bind to the adrenergic receptors and stimulate target organs just as sympathetic activity would. Other drugs are sympatholytic because they block adrenergic activity and cancel the sympathetic influence on the target organ. Drugs that act on the parasympathetic system also work by either enhancing the postganglionic signal or blocking it. A muscarinic agonist (or parasympathomimetic drug) acts just like ACh released by the parasympathetic postganglionic fiber. Anticholinergic drugs block muscarinic receptors, suppressing parasympathetic interaction with the organ.

Glossary

agonist

any exogenous substance that binds to a receptor and produces a similar effect to the endogenous ligand

antagonist

any exogenous substance that binds to a receptor and produces an opposing effect to the endogenous ligand

anticholinergic drugs

drugs that interrupt or reduce the function of the parasympathetic system

endogenous chemical

substance produced and released within the body to interact with a receptor protein

exogenous chemical

substance from a source outside the body, whether it be another organism such as a plant or from the synthetic processes of a laboratory, that binds to a transmembrane receptor protein

mydriasis

dilation of the pupil; typically the result of disease, trauma, or drugs

parasympathomimetic drugs

drugs that enhance or mimic the function of the parasympathetic system

sympatholytic drug

drug that interrupts, or "lyses," the function of the sympathetic system

sympathomimetic drug

drug that enhances or mimics the function of the sympathetic system

OU Human Physiology: Muscle Tissue Introduction class="introduction" Tennis Player



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Explain the organization of muscle tissue
- Describe the location, function, and structure of skeletal, cardiac, and smooth muscle
- Explain how muscles move bone
- Describe how muscles contract and relax
- Define the process of muscle metabolism
- Explain how the nervous system controls muscle tension
- Relate the connections between exercise and muscle performance

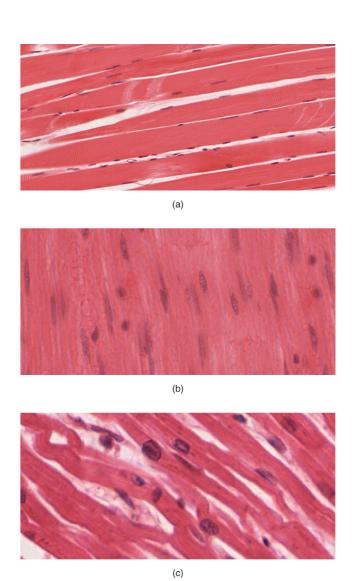
When most people think of muscles, they think of the muscles that are visible just under the skin, particularly of the limbs. These are skeletal muscles, so-named because most of them move the skeleton. But there are two other types of muscle in the body, with distinctly different jobs. Cardiac muscle, found in the heart, is concerned with pumping blood through the circulatory system. Smooth muscle is concerned with various involuntary movements, such as having one's hair stand on end when cold or frightened, or moving food through the digestive system. This chapter will examine the structure and function of these three types of muscles.

OU Human Physiology: Overview of Muscle Tissues By the end of this section, you will be able to:

- Explain the organization of muscle tissue from the macroscopic level down to the molecular level
- Describe the location, function, and structure of skeletal, cardiac, and smooth muscle
- Compare and contrast the sarcomere arrangement in skeletal, cardiac, and smooth muscle
- Differentiate myogenic from neurogenic muscle fibers

Muscle is one of the four primary tissue types of the body, and the body contains three types of muscle tissue: skeletal muscle, cardiac muscle, and smooth muscle ([link]). All three muscle tissues have some properties in common; they all exhibit a quality called **excitability** as their plasma membranes can change their electrical states (from polarized to depolarized) and send an electrical wave called an action potential along the entire length of the membrane. While the nervous system can influence the excitability of cardiac and smooth muscle to some degree, skeletal muscle completely depends on signaling from the nervous system to work properly. On the other hand, both cardiac muscle and smooth muscle can respond to other stimuli, such as hormones and local stimuli.

The Three Types of Muscle Tissue



The body contains three types of muscle tissue: (a) skeletal muscle, (b) smooth muscle, and (c) cardiac muscle. From top, LM × 1600, LM × 1600. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The muscles all begin the actual process of contracting (shortening) when a protein called actin is pulled by a protein called myosin. This occurs in

striated muscle (skeletal and cardiac) after specific binding sites on the actin have been exposed in response to the interaction between calcium ions (Ca⁺⁺) and proteins (troponin and tropomyosin) that "shield" the actinbinding sites. Ca⁺⁺ also is required for the contraction of smooth muscle, although its role is different: here Ca⁺⁺ activates enzymes, which in turn activate myosin heads. All muscles require adenosine triphosphate (ATP) to continue the process of contracting, and they all relax when the Ca⁺⁺ is removed and the actin-binding sites are re-shielded.

A muscle can return to its original length when relaxed due to a quality of muscle tissue called **elasticity**. It can recoil back to its original length due to elastic fibers. Muscle tissue also has the quality of **extensibility**; it can stretch or extend. **Contractility** allows muscle tissue to pull on its attachment points and shorten with force.

Differences among the three muscle types include the microscopic organization of their contractile proteins—actin and myosin. The actin and myosin proteins are arranged very regularly in the cytoplasm of individual muscle cells (referred to as fibers) in both skeletal muscle and cardiac muscle, which creates a pattern, or stripes, called striations. The striations are visible with a light microscope under high magnification (see [link]). **Skeletal muscle** fibers are multinucleated structures that compose the skeletal muscle. **Cardiac muscle** fibers each have one to two nuclei and are physically and electrically connected to each other so that the entire heart contracts as one unit (called a syncytium).

Because the actin and myosin are not arranged in such regular fashion in **smooth muscle**, the cytoplasm of a smooth muscle fiber (which has only a single nucleus) has a uniform, nonstriated appearance (resulting in the name smooth muscle). However, the less organized appearance of smooth muscle should not be interpreted as less efficient. Smooth muscle in the walls of arteries is a critical component that regulates blood pressure necessary to push blood through the circulatory system; and smooth muscle in the skin, visceral organs, and internal passageways is essential for moving all materials through the body.

Chapter Review

Muscle is the tissue in animals that allows for active movement of the body or materials within the body. There are three types of muscle tissue: skeletal muscle, cardiac muscle, and smooth muscle. Most of the body's skeletal muscle produces movement by acting on the skeleton. Cardiac muscle is found in the wall of the heart and pumps blood through the circulatory system.

Smooth muscle is found in the skin, where it is associated with hair follicles; it also is found in the walls of internal organs, blood vessels, and internal passageways, where it assists in moving materials.

Glossary

cardiac muscle

striated muscle found in the heart; joined to one another at intercalated discs and under the regulation of pacemaker cells, which contract as one unit to pump blood through the circulatory system. Cardiac muscle is under involuntary control.

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contractility
ability to shorten (contract) forcibly
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elasticity ability to stretch and rebound

excitability ability to undergo neural stimulation

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extensibility ability to lengthen (extend)
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skeletal muscle

striated, multinucleated muscle that requires signaling from the nervous system to trigger contraction; most skeletal muscles are referred to as voluntary muscles that move bones and produce movement

smooth muscle

nonstriated, mononucleated muscle in the skin that is associated with hair follicles; assists in moving materials in the walls of internal organs, blood vessels, and internal passageways

OU Human Physiology: Skeletal Muscle By the end of this section, you will be able to:

- Explain how muscles move bone
- Describe the structure and function of the thin filament
- Describe the structure and function of the thick filament
- Describe the sarcomere including all zones, discs, and bands and what myofilament composes these areas
- Describe the events occurring at the neuromuscular junction

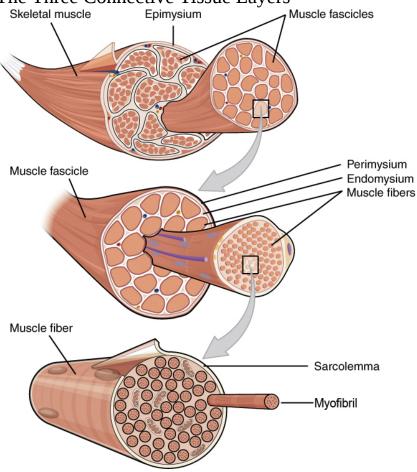
The best-known feature of skeletal muscle is its ability to contract and cause movement. Skeletal muscles act not only to produce movement but also to stop movement, such as resisting gravity to maintain posture. Small, constant adjustments of the skeletal muscles are needed to hold a body upright or balanced in any position. Muscles also prevent excess movement of the bones and joints, maintaining skeletal stability and preventing skeletal structure damage or deformation. Joints can become misaligned or dislocated entirely by pulling on the associated bones; muscles work to keep joints stable. Skeletal muscles are located throughout the body at the openings of internal tracts to control the movement of various substances. These muscles allow functions, such as swallowing, urination, and defecation, to be under voluntary control. Skeletal muscles also protect internal organs (particularly abdominal and pelvic organs) by acting as an external barrier or shield to external trauma and by supporting the weight of the organs.

Skeletal muscles contribute to the maintenance of homeostasis in the body by generating heat. Muscle contraction requires energy, and when ATP is broken down, heat is produced. This heat is very noticeable during exercise, when sustained muscle movement causes body temperature to rise, and in cases of extreme cold, when shivering produces random skeletal muscle contractions to generate heat.

Each skeletal muscle is an organ that consists of various integrated tissues. These tissues include the skeletal muscle fibers, blood vessels, nerve fibers, and connective tissue. Each skeletal muscle has three layers of connective tissue (called "mysia") that enclose it and provide structure to the muscle as a whole, and also compartmentalize the muscle fibers within the muscle

([link]). Each muscle is wrapped in a sheath of dense, irregular connective tissue called the **epimysium**, which allows a muscle to contract and move powerfully while maintaining its structural integrity. The epimysium also separates muscle from other tissues and organs in the area, allowing the muscle to move independently.

The Three Connective Tissue Layers



Bundles of muscle fibers, called fascicles, are covered by the perimysium. Muscle fibers are covered by the endomysium.

Inside each skeletal muscle, muscle fibers are organized into individual bundles, each called a **fascicle**, by a middle layer of connective tissue called the **perimysium**. This fascicular organization is common in muscles of the limbs; it allows the nervous system to trigger a specific movement of a

muscle by activating a subset of muscle fibers within a bundle, or fascicle of the muscle. Inside each fascicle, each muscle fiber is encased in a thin connective tissue layer of collagen and reticular fibers called the **endomysium**. The endomysium contains the extracellular fluid and nutrients to support the muscle fiber. These nutrients are supplied via blood to the muscle tissue.

Each muscle fiber is composed of many myofibrils. Myofibrils contain many sarcomeres. Sarcomeres are the fundamental unit of skeletal muscle (see [link]). Sarcomeres are composed of thick and thin myofilaments called myosin and actin, respectively. Actin and myosin are contractile proteins which are responsible for muscle contraction (see [link]).

Every skeletal muscle is also richly supplied by blood vessels for nourishment, oxygen delivery, and waste removal. In addition, every muscle fiber in a skeletal muscle is supplied by the axon branch of a somatic motor neuron, which signals the fiber to contract. Unlike cardiac and smooth muscle, the only way to functionally contract a skeletal muscle is through signaling from the nervous system.

Skeletal Muscle Fibers

Because skeletal muscle cells are long and cylindrical, they are commonly referred to as muscle fibers. Skeletal muscle fibers can be quite large for human cells, with diameters up to $100~\mu m$ and lengths up to 30~cm (11.8 in) in the Sartorius of the upper leg. During early development, embryonic myoblasts, each with its own nucleus, fuse with up to hundreds of other myoblasts to form the multinucleated skeletal muscle fibers. Multiple nuclei mean multiple copies of genes, permitting the production of the large amounts of proteins and enzymes needed for muscle contraction.

Some other terminology associated with muscle fibers is rooted in the Greek *sarco*, which means "flesh." The plasma membrane of muscle fibers is called the **sarcolemma**, the cytoplasm is referred to as **sarcoplasm**. The sarcoplasm stores glycogen and myoglobin and contains many mitochondria. The specialized smooth endoplasmic reticulum, which stores, releases, and retrieves calcium ions (Ca⁺⁺) is called the **sarcoplasmic**

reticulum (SR) ([link]). As will soon be described, the functional unit of a skeletal muscle fiber is the sarcomere, a highly organized arrangement of the contractile myofilaments **actin** (thin filament) and **myosin** (thick filament), along with other support proteins.

Muscle Fiber Nucleus Muscle fiber Mitochondrion Sarcolemma Light I band Myofibril Dark A band Sarcoplasmic Sarcomere reticulum Thin (actin) Thick (myosin) filament Z disc Z disc filament H zone

A skeletal muscle fiber is surrounded by a plasma membrane called the sarcolemma, which contains sarcoplasm, the cytoplasm of muscle cells. A muscle fiber is composed of many myofibrils.

A band

I band

M line

I band

The Sarcomere

The striated appearance of skeletal muscle fibers is due to the arrangement of the myofilaments of actin and myosin in sequential order from one end of the muscle fiber to the other. Each packet of these myofilaments and their regulatory proteins, **troponin** and **tropomyosin** (along with other proteins) is called a **sarcomere**.

Note:



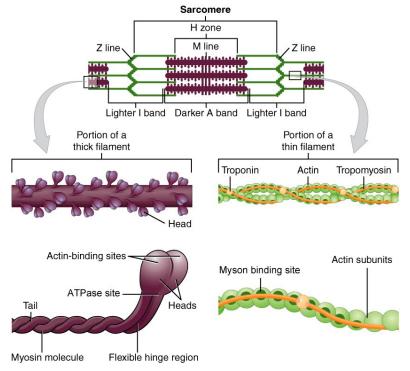
Watch this <u>video</u> to learn more about macro- and microstructures of skeletal muscles. (a) What are the names of the "junction points" between sarcomeres? (b) What are the names of the "subunits" within the myofibrils that run the length of skeletal muscle fibers? (c) What is the "double strand of pearls" described in the video? (d) What gives a skeletal muscle fiber its striated appearance?

The sarcomere is the functional unit of the muscle fiber. The sarcomere itself is bundled within the myofibril that runs the entire length of the muscle fiber and attaches to the sarcolemma at its end. As myofibrils contract, the entire muscle cell contracts. Because myofibrils are only approximately 1.2 μ m in diameter, hundreds to thousands (each with thousands of sarcomeres) can be found inside one muscle fiber. Each sarcomere is approximately 2 μ m in length with a three-dimensional cylinder-like arrangement and is bordered by structures called Z-discs (also called Z-lines, because pictures are two-dimensional), to which the actin myofilaments are anchored ([link]). Because the actin and its troponintropomyosin complex (projecting from the Z-discs toward the center of the sarcomere) form strands that are thinner than the myosin, it is called the thin filament of the sarcomere. Likewise, because the myosin strands and their multiple heads (projecting from the center of the sarcomere, toward but not all to way to, the Z-discs) have more mass and are thicker, they are called the **thick filament** of the sarcomere.

The sarcomere is also divided into several "zones," "bands," and "lines" (see [link]) The A band contains both thick and thin myofilaments. The H zone is the center of the A band and consists of only thick myofilaments.

The M-line bisects the A band vertically and passes through the center of the H zone. The I band contains thin myofilaments only.

The Sarcomere



The sarcomere, the region from one Z-line to the next Z-line, is the functional unit of a skeletal muscle fiber.

The Neuromuscular Junction

Another specialization of the skeletal muscle is the site where a motor neuron's terminal meets the muscle fiber—called the **neuromuscular junction (NMJ)**. This is where the muscle fiber first responds to signaling by the motor neuron. Every skeletal muscle fiber in every skeletal muscle is innervated by a motor neuron at the NMJ. Excitation signals from the neuron are the only way to functionally activate the fiber to contract.

Note:



Every skeletal muscle fiber is supplied by a motor neuron at the NMJ. Watch this <u>video</u> to learn more about what happens at the NMJ. (a) What is the definition of a motor unit? (b) What is the structural and functional difference between a large motor unit and a small motor unit? (c) Can you give an example of each? (d) Why is the neurotransmitter acetylcholine degraded after binding to its receptor?

Excitation-Contraction Coupling

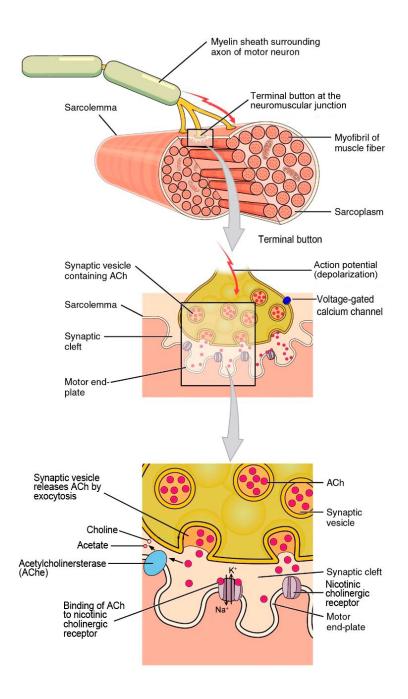
All living cells have membrane potentials, or electrical gradients across their membranes. The inside of the membrane is usually around -60 to -90 mV, relative to the outside. This is referred to as a cell's membrane potential. Neurons and muscle cells can use their membrane potentials to generate electrical signals. They do this by controlling the movement of charged particles, called ions, across their membranes to create electrical currents. This is achieved by opening and closing specialized proteins in the membrane called ion channels. Although the currents generated by ions moving through these channel proteins are very small, they form the basis of both neural signaling and muscle contraction.

Both neurons and skeletal muscle cells are electrically excitable, meaning that they are able to generate action potentials. An action potential is a special type of electrical signal that can travel along a cell membrane as a wave. This allows a signal to be transmitted quickly and faithfully over long distances.

Although the term **excitation-contraction coupling** confuses or scares some students, it comes down to this: for a skeletal muscle fiber to contract, its membrane must first be "excited"—in other words, it must be stimulated to fire an action potential. The muscle fiber action potential, which sweeps along the sarcolemma as a wave, is "coupled" to the actual contraction through the release of calcium ions (Ca⁺⁺) from the SR. Once released, the Ca⁺⁺ interacts with the shielding proteins, forcing them to move aside so that the actin-binding sites are available for attachment by myosin heads. The myosin then pulls the actin filaments toward the center, shortening the muscle fiber.

In skeletal muscle, this sequence begins with signals from the somatic motor division of the nervous system. In other words, the "excitation" step in skeletal muscles is always triggered by signaling from the nervous system ([link]).

Motor End-Plate and Innervation



When depolarization spreads down the motor neuron (axon) and into the terminal button, this change in the membrane potential will cause voltage-gated calcium channels on the membrane of the terminal button to open. Once open, calcium influx will occur resulting in exocytosis of the synaptic vesicle containing ACh. ACh

will then diffuse across the synaptic cleft and bind to nicotinic cholinergic receptors. The nicotinic cholinergic receptors generate fast responses and as a result when ACh binds, the channel opens and sodium influx occurs and potassium efflux. There is a greater driving force for sodium than potassium efflux and influx ????????

The motor neurons that tell the skeletal muscle fibers to contract originate in the spinal cord, with a smaller number located in the brainstem for activation of skeletal muscles of the face, head, and neck. These neurons have long processes, called axons, which are specialized to transmit action potentials long distances— in this case, all the way from the spinal cord to the muscle itself (which may be up to three feet away). The axons of multiple neurons bundle together to form nerves, like wires bundled together in a cable.

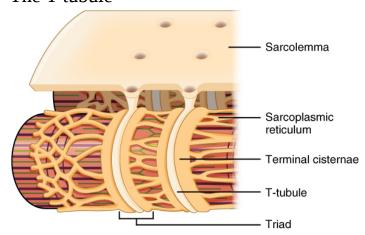
Signaling begins when a neuronal **action potential** travels along the axon of a motor neuron, and then along the individual branches to terminate at the NMJ. At the NMJ, the axon terminal releases a chemical messenger, or **neurotransmitter**, called **acetylcholine** (**ACh**). The ACh molecules diffuse across a minute space called the **synaptic cleft** and bind to nicotinic cholinergic receptors located within the **motor end-plate** of the sarcolemma on the other side of the synapse. Nicotinic cholinergic receptors area a type of ionotropic channel and therefore generate fast responses since the receptor and the channel are the same protein. Once ACh binds, the channel opens allowing sodium influx and potassium efflux. There is a greater current for sodium than potassium due to the higher driving force for sodium. As a result of the greater movement of sodium into the cell, the motor end plate depolarizes. This depolarization is called an end plate potential (a type of graded potential).

As the membrane depolarizes, another set of ion channels called **voltage-gated sodium channels** are triggered to open. Sodium ions enter the muscle fiber, and an action potential rapidly spreads (or "fires") along the entire membrane to initiate excitation-contraction coupling.

Things happen very quickly in the world of excitable membranes (just think about how quickly you can snap your fingers as soon as you decide to do it). Immediately following depolarization of the membrane, it repolarizes, re-establishing the negative membrane potential. Meanwhile, the ACh in the synaptic cleft is degraded by the enzyme acetylcholinesterase (AChE) so that the ACh cannot rebind to a receptor and reopen its channel, which would cause unwanted extended muscle excitation and contraction.

Propagation of an action potential along the sarcolemma is the excitation portion of excitation-contraction coupling. Recall that this excitation actually triggers the release of calcium ions (Ca^{++}) from its storage in the cell's SR. For the action potential to reach the membrane of the SR, there are periodic invaginations in the sarcolemma, called **T-tubules** ("T" stands for "transverse"). You will recall that the diameter of a muscle fiber can be up to $100 \, \mu \text{m}$, so these T-tubules ensure that the membrane can get close to the SR in the sarcoplasm. The arrangement of a T-tubule with the membranes of SR on either side is called a **triad** ([link]). The triad surrounds the cylindrical structure called a **myofibril**, which contains actin and myosin.

The T-tubule



Narrow T-tubules permit the conduction of electrical impulses. The

SR functions to regulate intracellular levels of calcium. Two terminal cisternae (where enlarged SR connects to the T-tubule) and one T-tubule comprise a triad—a "threesome" of membranes, with those of SR on two sides and the T-tubule sandwiched between them.

The T-tubules carry the action potential into the interior of the cell, which ultimately triggers the opening of calcium channels in the membrane of the adjacent SR, causing Ca⁺⁺ to diffuse out of the SR and into the sarcoplasm. It is the arrival of Ca⁺⁺ in the sarcoplasm that initiates contraction of the muscle fiber by its contractile units, or sarcomeres.

Chapter Review

Skeletal muscles contain connective tissue, blood vessels, and nerves. There are three layers of connective tissue: epimysium, perimysium, and endomysium. Skeletal muscle fibers are organized into groups called fascicles. Blood vessels and nerves enter the connective tissue and branch in the cell. Muscles attach to bones directly or through tendons or aponeuroses. Skeletal muscles maintain posture, stabilize bones and joints, control internal movement, and generate heat.

Skeletal muscle fibers are long, multinucleated cells. The membrane of the cell is the sarcolemma; the cytoplasm of the cell is the sarcoplasm. The sarcoplasmic reticulum (SR) is a form of endoplasmic reticulum. Muscle fibers are composed of myofibrils. The striations are created by the organization of actin and myosin resulting in the banding pattern of myofibrils.

Glossary

acetylcholine (ACh)

neurotransmitter that binds at a motor end-plate to trigger depolarization

actin

protein that makes up most of the thin myofilaments in a sarcomere muscle fiber

action potential

change in voltage of a cell membrane in response to a stimulus that results in transmission of an electrical signal; unique to neurons and muscle fibers

endomysium

loose, and well-hydrated connective tissue covering each muscle fiber in a skeletal muscle

epimysium

outer layer of connective tissue around a skeletal muscle

excitation-contraction coupling

sequence of events from motor neuron signaling to a skeletal muscle fiber to contraction of the fiber's sarcomeres

fascicle

bundle of muscle fibers within a skeletal muscle

motor end-plate

sarcolemma of muscle fiber at the neuromuscular junction, with receptors for the neurotransmitter acetylcholine

myofibril

long, cylindrical organelle that runs parallel within the muscle fiber and contains the sarcomeres

myosin

protein that makes up most of the thick cylindrical myofilament within a sarcomere muscle fiber

neuromuscular junction (NMJ)

synapse between the axon terminal of a motor neuron and the section of the membrane of a muscle fiber with receptors for the acetylcholine released by the terminal

neurotransmitter

signaling chemical released by nerve terminals that bind to and activate receptors on target cells

perimysium

connective tissue that bundles skeletal muscle fibers into fascicles within a skeletal muscle

sarcolemma

plasma membrane of a skeletal muscle fiber

sarcoplasm

cytoplasm of a muscle cell

sarcomere

longitudinally, repeating functional unit of skeletal muscle, with all of the contractile and associated proteins involved in contraction

sarcoplasmic reticulum (SR)

specialized smooth endoplasmic reticulum, which stores, releases, and retrieves Ca⁺⁺

synaptic cleft

space between a nerve (axon) terminal and a motor end-plate

T-tubule

projection of the sarcolemma into the interior of the cell

thick filament

the thick myosin strands and their multiple heads projecting from the center of the sarcomere toward, but not all to way to, the Z-discs

thin filament

thin strands of actin and its troponin-tropomyosin complex projecting from the Z-discs toward the center of the sarcomere

triad

the grouping of one T-tubule and two terminal cisternae

troponin

regulatory protein that binds to actin, tropomyosin, and calcium

tropomyosin

regulatory protein that covers myosin-binding sites to prevent actin from binding to myosin

troponin

regulatory protein that binds to actin, tropomyosin, and calcium

voltage-gated sodium channels

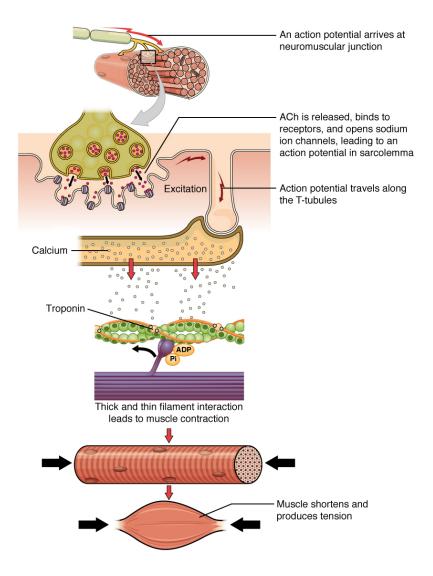
membrane proteins that open sodium channels in response to a sufficient voltage change, and initiate and transmit the action potential as Na⁺ enters through the channel

OU Human Physiology: Muscle Fiber Contraction and Relaxation By the end of this section, you will be able to:

- Explain the events of cross bridge cycling
- Explain the events of excitation-contraction coupling in skeletal muscle
- Explain the events of relaxation in skeletal muscle
- Describe the sliding filament theory and the changes in the sarcomere during muscle contraction
- List the three sources of ATP and describe the mechanism for each including circumstances in which each would be utilized

The sequence of events that result in the contraction of an individual muscle fiber begins with a signal—the neurotransmitter, ACh—from the motor neuron innervating that fiber. The local membrane of the fiber will depolarize as positively charged sodium ions (Na⁺) enter, triggering an action potential that spreads to the rest of the membrane and down the T-tubules. The change in the membrane potential will trigger the dihydropyridine (DHP) receptors on the T-tubules. The DHP receptors are voltage-gated "sensors" which change shape causing the ryanodine channels on the SR to open. This triggers the release of calcium ions (Ca⁺⁺) from storage in the sarcoplasmic reticulum (SR). The Ca⁺⁺ then initiates contraction, which is sustained by ATP ([link]). As long as Ca⁺⁺ ions remain in the sarcoplasm to bind to troponin, which keeps the actin-binding sites "exposed," and as long as ATP is available to drive the cross-bridge cycling and the pulling of actin strands by myosin, the muscle fiber will continue to shorten (contract).

Contraction of a Muscle Fiber

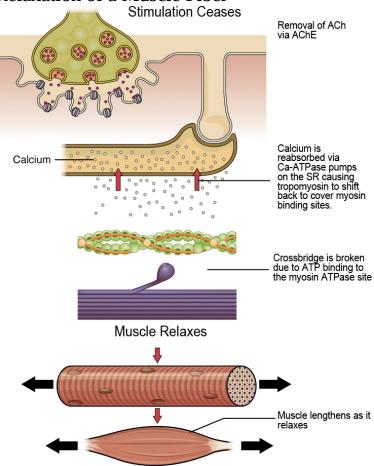


A cross-bridge forms between actin and the myosin heads triggering contraction. As long as Ca⁺⁺ ions remain in the sarcoplasm to bind to troponin, and as long as ATP is available, the muscle fiber will continue to shorten.

Muscle contraction usually stops when signaling from the motor neuron ends, which repolarizes the sarcolemma and T-tubules, and closes the voltage-gated calcium channels in the SR. Ca-ATPase pumps (a type of primary active transport) are located on the membrane of the SR. These

pumps are always pumping calcium ions from the sarcoplasm into the SR. When the signal from the motor neuron stops and the Ca-ATPase pumps continues to reuptake calcium ions into the SR, the concentration of calcium ions in the sarcoplasm decreases which stimulates calcium ions to be removed from troponin causing tropomyosin to shift back covering the myosin binding sites. A muscle also can stop contracting when it runs out of ATP and becomes fatigued ([link]).

Relaxation of a Muscle Fiber



Ca⁺⁺ ions are pumped back into the SR, which causes the tropomyosin to reshield the myosin binding sites on the actin. A muscle may also stop contracting when it runs out of ATP and becomes fatigued.

Note:



The release of calcium ions initiates muscle contractions. Watch this <u>video</u> to learn more about the role of calcium. (a) What are "T-tubules" and what is their role? (b) Please describe how actin-binding sites are made available for cross-bridging with myosin heads during contraction.

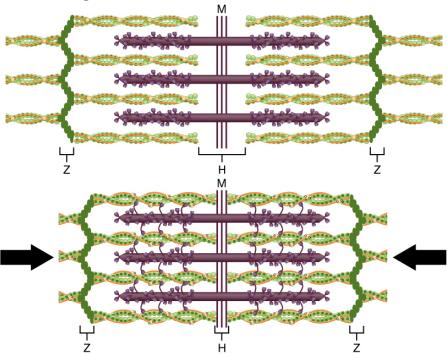
The molecular events of muscle fiber shortening occur within the fiber's sarcomeres (see [link]). The contraction of a striated muscle fiber occurs as the sarcomeres, linearly arranged within myofibrils, shorten as myosin heads pull on the actin filaments.

The region where thick and thin filaments overlap has a dense appearance, as there is little space between the filaments. This zone where thin and thick filaments overlap is very important to muscle contraction, as it is the site where filament movement starts. Thin filaments, anchored at their ends by the Z-discs, do not extend completely into the central region that only contains thick filaments, anchored at their bases at a spot called the M-line. A myofibril is composed of many sarcomeres running along its length; thus, myofibrils and muscle cells contract as the sarcomeres contract.

The Sliding Filament Model of Contraction

When signaled by a motor neuron, a skeletal muscle fiber contracts as the thin filaments are pulled and then slide past the thick filaments within the fiber's sarcomeres. This process is known as the sliding filament model of muscle contraction ([link]). The sliding can only occur when myosin-binding sites on the actin filaments are exposed by a series of steps that begins with Ca⁺⁺ entry into the sarcoplasm.

The Sliding Filament Model of Muscle Contraction



When a sarcomere contracts, the Z lines move closer together, the I band becomes smaller, and the H zone practically disappears. The A band stays the same width but the A bands between adjacent sarcomeres are closer together. At full contraction, the thin and thick filaments overlap.

Tropomyosin is a protein that winds around the chains of the actin filament and covers the myosin-binding sites to prevent actin from binding to myosin. Tropomyosin binds to troponin to form a troponin-tropomyosin complex. The troponin-tropomyosin complex prevents the myosin "heads" from binding to the active sites on the actin microfilaments. Troponin also has a binding site for Ca⁺⁺ ions.

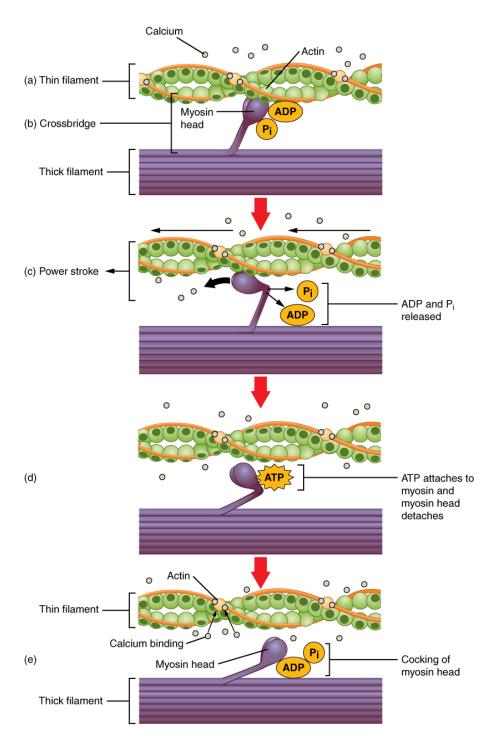
To initiate muscle contraction, tropomyosin has to expose the myosin-binding site on an actin filament to allow cross-bridge formation between the actin and myosin microfilaments. The first step in the process of contraction is for Ca⁺⁺ to bind to troponin so that tropomyosin can slide

away from the binding sites on the actin strands. This allows the myosin heads to bind to these exposed binding sites and form cross-bridges. The thin filaments are then pulled by the myosin heads to slide past the thick filaments toward the center of the sarcomere. But each head can only pull a very short distance before it has reached its limit and must be "re-cocked" before it can pull again, a step that requires ATP.

ATP and Muscle Contraction

For thin filaments to continue to slide past thick filaments during muscle contraction, myosin heads must pull the actin at the binding sites, detach, re-cock, attach to more binding sites, pull, detach, re-cock, etc. This repeated movement is known as the cross-bridge cycle. This motion of the myosin heads is similar to the oars when an individual rows a boat: The paddle of the oars (the myosin heads) pull, are lifted from the water (detach), repositioned (re-cocked) and then immersed again to pull ([link]). Each cycle requires energy, and the action of the myosin heads in the sarcomeres repetitively pulling on the thin filaments also requires energy, which is provided by ATP.

Skeletal Muscle Contraction



(a) The active site on actin is exposed as calcium binds to troponin. (b) The myosin head is attracted to actin, and myosin binds actin at its actin-binding site, forming the cross-bridge. (c) During the power stroke, the phosphate generated in the previous contraction cycle is released. This results

in the myosin head pivoting toward the center of the sarcomere, after which the attached ADP and phosphate group are released. (d) A new molecule of ATP attaches to the myosin head, causing the cross-bridge to detach. (e) The myosin head hydrolyzes ATP to ADP and phosphate, which returns the myosin to the cocked position.

Cross-bridge formation occurs when the myosin head attaches to the actin while adenosine diphosphate (ADP) and inorganic phosphate (P_i) are still bound to myosin ($[\underline{link}]a,b$). P_i is then released, causing myosin to form a stronger attachment to the actin, after which the myosin head moves toward the M-line, pulling the actin along with it. As actin is pulled, the filaments move approximately 10 nm toward the M-line. This movement is called the **power stroke**, as movement of the thin filament occurs at this step ($[\underline{link}]c$). In the absence of ATP, the myosin head will not detach from actin.

One part of the myosin head attaches to the binding site on the actin, but the head has another binding site for ATP. ATP binding causes the myosin head to detach from the actin ($[\underline{link}]d$). After this occurs, ATP is converted to ADP and P_i by the intrinsic **ATPase** activity of myosin. The energy released during ATP hydrolysis changes the angle of the myosin head into a cocked position ($[\underline{link}]e$). The myosin head is now in position for further movement.

When the myosin head is cocked, myosin is in a high-energy configuration. This energy is expended as the myosin head moves through the power stroke, and at the end of the power stroke, the myosin head is in a low-energy position. After the power stroke, ADP is released; however, the formed cross-bridge is still in place, and actin and myosin are bound together. As long as ATP is available, it readily attaches to myosin, the cross-bridge cycle can recur, and muscle contraction can continue.

Note that each thick filament of roughly 300 myosin molecules has multiple myosin heads, and many cross-bridges form and break continuously during

muscle contraction. Multiply this by all of the sarcomeres in one myofibril, all the myofibrils in one muscle fiber, and all of the muscle fibers in one skeletal muscle, and you can understand why so much energy (ATP) is needed to keep skeletal muscles working. In fact, it is the loss of ATP that results in the rigor mortis observed soon after someone dies. With no further ATP production possible, there is no ATP available for myosin heads to detach from the actin-binding sites, so the cross-bridges stay in place, causing the rigidity in the skeletal muscles.

Note:



Watch this <u>video</u> to learn more about the crossbridge cycle.

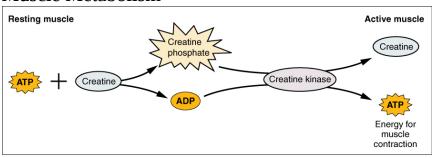
Sources of ATP

ATP supplies the energy for muscle contraction to take place. In addition to its direct role in the cross-bridge cycle, ATP also provides the energy for the active-transport Ca⁺⁺ pumps in the SR. Muscle contraction does not occur without sufficient amounts of ATP. The amount of ATP stored in muscle is very low, only sufficient to power a few seconds worth of contractions. As it is broken down, ATP must therefore be regenerated and replaced quickly to allow for sustained contraction. There are three mechanisms by which ATP can be regenerated: creatine phosphate metabolism, anaerobic glycolysis, fermentation and aerobic respiration.

Creatine phosphate is a molecule that can store energy in its phosphate bonds. In a resting muscle, excess ATP transfers its energy to creatine, producing ADP and creatine phosphate. This acts as an energy reserve that

can be used to quickly create more ATP. When the muscle starts to contract and needs energy, creatine phosphate transfers its phosphate back to ADP to form ATP and creatine. This reaction is catalyzed by the enzyme creatine kinase and occurs very quickly; thus, creatine phosphate-derived ATP powers the first few seconds of muscle contraction. However, creatine phosphate can only provide approximately 15 seconds worth of energy, at which point another energy source has to be used ([link]).

Muscle Metabolism



Glucose

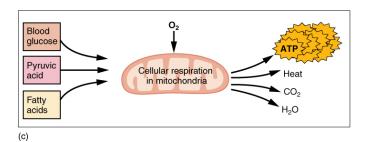
Glycolysis

Aerobic respiration

Oxygen

No Oxygen

Lactic acid to blood



(a) Some ATP is stored in a resting muscle. As contraction starts, it is used up in seconds. More ATP is generated from creatine phosphate for about 15 seconds. (b) Each glucose molecule produces two ATP and two molecules of pyruvic acid, which can be used in aerobic respiration or converted to lactic acid. If oxygen

is not available, pyruvic acid is converted to lactic acid, which may contribute to muscle fatigue. This occurs during strenuous exercise when high amounts of energy are needed but oxygen cannot be sufficiently delivered to muscle. (c) Aerobic respiration is the breakdown of glucose in the presence of oxygen (O₂) to produce carbon dioxide, water, and ATP. Approximately 95 percent of the ATP required for resting or moderately active muscles is provided by aerobic respiration, which takes place in mitochondria.

As the ATP produced by creatine phosphate is depleted, muscles turn to glycolysis as an ATP source. **Glycolysis** is an anaerobic (non-oxygen-dependent) process that breaks down glucose (sugar) to produce ATP; however, glycolysis cannot generate ATP as quickly as creatine phosphate. Thus, the switch to glycolysis results in a slower rate of ATP availability to the muscle. The sugar used in glycolysis can be provided by blood glucose or by metabolizing glycogen that is stored in the muscle. The breakdown of one glucose molecule produces two ATP and two molecules of **pyruvic acid**, which can be used in aerobic respiration or when oxygen levels are low, converted to lactic acid ([link]b).

If oxygen is available, pyruvic acid is used in aerobic respiration. However, if oxygen is not available, pyruvic acid is converted to **lactic acid**, which may contribute to muscle fatigue. This conversion allows the recycling of the enzyme NAD⁺ from NADH, which is needed for glycolysis to continue. This occurs during strenuous exercise when high amounts of energy are needed but oxygen cannot be sufficiently delivered to muscle. Glycolysis itself cannot be sustained for very long (approximately 1 minute of muscle activity), but it is useful in facilitating short bursts of high-intensity output. This is because glycolysis does not utilize glucose very efficiently, producing a net gain of two ATPs per molecule of glucose, and the end

product of lactic acid, which may contribute to muscle fatigue as it accumulates.

Aerobic respiration is the breakdown of glucose or other nutrients in the presence of oxygen (O_2) to produce carbon dioxide, water, and ATP. Approximately 95 percent of the ATP required for resting or moderately active muscles is provided by aerobic respiration, which takes place in mitochondria. The inputs for aerobic respiration include glucose circulating in the bloodstream, pyruvic acid, and fatty acids. Aerobic respiration is much more efficient than anaerobic glycolysis, producing approximately 36 ATPs per molecule of glucose versus four from glycolysis. However, aerobic respiration cannot be sustained without a steady supply of O_2 to the skeletal muscle and is much slower ([link]c). To compensate, muscles store small amount of excess oxygen in proteins call myoglobin, allowing for more efficient muscle contractions and less fatigue. Aerobic training also increases the efficiency of the circulatory system so that O_2 can be supplied to the muscles for longer periods of time.

Muscle fatigue occurs when a muscle can no longer contract in response to signals from the nervous system. The exact causes of muscle fatigue are not fully known, although certain factors have been correlated with the decreased muscle contraction that occurs during fatigue. ATP is needed for normal muscle contraction, and as ATP reserves are reduced, muscle function may decline. This may be more of a factor in brief, intense muscle output rather than sustained, lower intensity efforts. Lactic acid buildup may lower intracellular pH, affecting enzyme and protein activity. Imbalances in Na⁺ and K⁺ levels as a result of membrane depolarization may disrupt Ca⁺⁺ flow out of the SR. Long periods of sustained exercise may damage the SR and the sarcolemma, resulting in impaired Ca⁺⁺ regulation.

Intense muscle activity results in an **oxygen debt**, which is the amount of oxygen needed to compensate for ATP produced without oxygen during muscle contraction. Oxygen is required to restore ATP and creatine phosphate levels, convert lactic acid to pyruvic acid, and, in the liver, to convert lactic acid into glucose or glycogen. Other systems used during exercise also require oxygen, and all of these combined processes result in

the increased breathing rate that occurs after exercise. Until the oxygen debt has been met, oxygen intake is elevated, even after exercise has stopped.

Relaxation of a Skeletal Muscle

Relaxing skeletal muscle fibers, and ultimately, the skeletal muscle, begins with the motor neuron, which stops releasing its chemical signal, ACh, into the synapse at the NMJ. The muscle fiber will repolarize, which closes the gates in the SR where Ca⁺⁺ was being released. ATP-driven pumps will move Ca⁺⁺ out of the sarcoplasm back into the SR. This results in the "reshielding" of the actin-binding sites on the thin filaments. Without the ability to form cross-bridges between the thin and thick filaments, the muscle fiber loses its tension and relaxes.

Muscle Strength

The number of skeletal muscle fibers in a given muscle is genetically determined and does not change. Muscle strength is directly related to the amount of myofibrils and sarcomeres within each fiber. Factors, such as hormones and stress (and artificial anabolic steroids), acting on the muscle can increase the production of sarcomeres and myofibrils within the muscle fibers, a change called hypertrophy, which results in the increased mass and bulk in a skeletal muscle. Likewise, decreased use of a skeletal muscle results in atrophy, where the number of sarcomeres and myofibrils disappear (but not the number of muscle fibers). It is common for a limb in a cast to show atrophied muscles when the cast is removed, and certain diseases, such as polio, show atrophied muscles.

Note:

Disorders of the ...

Muscular System

Duchenne muscular dystrophy (DMD) is a progressive weakening of the skeletal muscles. It is one of several diseases collectively referred to as "muscular dystrophy." DMD is caused by a lack of the protein dystrophin, which helps the thin filaments of myofibrils bind to the sarcolemma.

Without sufficient dystrophin, muscle contractions cause the sarcolemma to tear, causing an influx of Ca⁺⁺, leading to cellular damage and muscle fiber degradation. Over time, as muscle damage accumulates, muscle mass is lost, and greater functional impairments develop.

DMD is an inherited disorder caused by an abnormal X chromosome. It primarily affects males, and it is usually diagnosed in early childhood. DMD usually first appears as difficulty with balance and motion, and then progresses to an inability to walk. It continues progressing upward in the body from the lower extremities to the upper body, where it affects the muscles responsible for breathing and circulation. It ultimately causes death due to respiratory failure, and those afflicted do not usually live past their 20s.

Because DMD is caused by a mutation in the gene that codes for dystrophin, it was thought that introducing healthy myoblasts into patients might be an effective treatment. Myoblasts are the embryonic cells responsible for muscle development, and ideally, they would carry healthy genes that could produce the dystrophin needed for normal muscle contraction. This approach has been largely unsuccessful in humans. A recent approach has involved attempting to boost the muscle's production of utrophin, a protein similar to dystrophin that may be able to assume the role of dystrophin and prevent cellular damage from occurring.

Chapter Review

A sarcomere is the smallest contractile portion of a muscle. Myofibrils are composed of thick and thin filaments. Thick filaments are composed of the protein myosin; thin filaments are composed of the protein actin. Troponin and tropomyosin are regulatory proteins.

Muscle contraction is described by the sliding filament model of contraction. ACh is the neurotransmitter that binds at the neuromuscular junction (NMJ) to trigger depolarization, and an action potential travels along the sarcolemma to trigger calcium release from SR. The actin sites are exposed after Ca⁺⁺ enters the sarcoplasm from its SR storage to activate the troponin-tropomyosin complex so that the tropomyosin shifts away

from the sites. The cross-bridging of myposin heads docking into actinbinding sites is followed by the "power stroke"—the sliding of the thin filaments by thick filaments. The power strokes are powered by ATP. Ultimately, the sarcomeres, myofibrils, and muscle fibers shorten to produce movement.

Glossary

aerobic respiration production of ATP in the presence of oxygen

ATPase

enzyme that hydrolyzes ATP to ADP

creatine phosphate

phosphagen used to store energy from ATP and transfer it to muscle

glycolysis

anaerobic breakdown of glucose to ATP

lactic acid

product of anaerobic glycolysis

oxygen debt

amount of oxygen needed to compensate for ATP produced without oxygen during muscle contraction

power stroke

action of myosin pulling actin inward (toward the M line)

pyruvic acid

product of glycolysis that can be used in aerobic respiration or converted to lactic acid

OU Human Physiology: Nervous System Control of Muscle Tension By the end of this section, you will be able to:

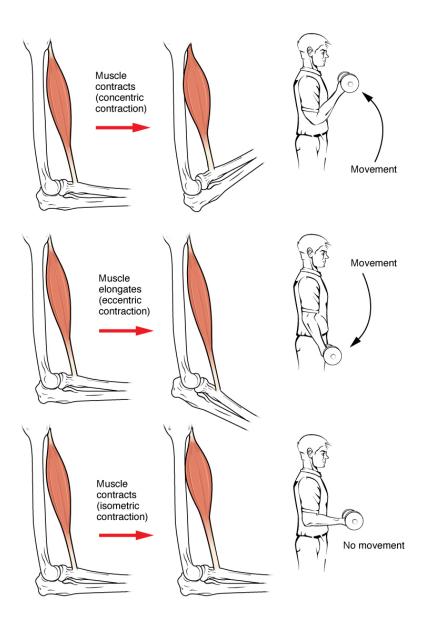
- Compare and contrast isotonic and isometric contractions
- Compare and contrast concentric isotonic and eccentric isotonic contractions
- Compare and contrast the factors (motor unit recruitment and size principle) affecting the force generated by whole muscle
- Explain the length tension curve and its relevance to muscle fibers
- Analyze a myogram of a muscle twitch
- List the phases of a muscle twitch
- Infer the events of excitation contraction coupling to the phases of the muscle twitch
- Compare and contrast the factors (treppe, summation, incomplete and complete tetanus) affecting the force generated by individual skeletal muscle fibers

To move an object, referred to as load, the sarcomeres in the muscle fibers of the skeletal muscle must shorten. The force generated by the contraction of the muscle (or shortening of the sarcomeres) is called **muscle tension**. However, muscle tension also is generated when the muscle is contracting against a load that does not move, resulting in two main types of skeletal muscle contractions: isotonic contractions and isometric contractions.

In **isotonic contractions**, where the tension in the muscle stays constant, a load is moved as the length of the muscle changes (shortens). There are two types of isotonic contractions: concentric and eccentric. A **concentric contraction** involves the muscle shortening to move a load. An example of this is the biceps brachii muscle contracting when a hand weight is brought upward with increasing muscle tension. As the biceps brachii contract, the angle of the elbow joint decreases as the forearm is brought toward the body. Here, the biceps brachii contracts as sarcomeres in its muscle fibers are shortening and cross-bridges form; the myosin heads pull the actin. An **eccentric contraction** occurs as the muscle tension diminishes and the muscle lengthens. In this case, the hand weight is lowered in a slow and controlled manner as the amount of cross-bridges being activated by nervous system stimulation decreases. In this case, as tension is released

from the biceps brachii, the angle of the elbow joint increases. Eccentric contractions are also used for movement and balance of the body.

An **isometric contraction** occurs as the muscle produces tension without changing the angle of a skeletal joint. Isometric contractions involve sarcomere shortening and increasing muscle tension, but do not move a load, as the force produced cannot overcome the resistance provided by the load. For example, if one attempts to lift a hand weight that is too heavy, there will be sarcomere activation and shortening to a point, and everincreasing muscle tension, but no change in the angle of the elbow joint. In everyday living, isometric contractions are active in maintaining posture and maintaining bone and joint stability. However, holding your head in an upright position occurs not because the muscles cannot move the head, but because the goal is to remain stationary and not produce movement. Most actions of the body are the result of a combination of isotonic and isometric contractions working together to produce a wide range of outcomes ([link]). Types of Muscle Contractions



During isotonic contractions, muscle length changes to move a load. During isometric contractions, muscle length does not change because the load exceeds the tension the muscle can generate.

All of these muscle activities are under the exquisite control of the nervous system. Neural control regulates concentric, eccentric and isometric

contractions, muscle fiber recruitment, and muscle tone. A crucial aspect of nervous system control of skeletal muscles is the role of motor units.

Motor Units

As you have learned, every skeletal muscle fiber must be innervated by the axon terminal of a motor neuron in order to contract. Each muscle fiber is innervated by only one motor neuron. The actual group of muscle fibers in a muscle innervated by a single motor neuron is called a **motor unit**. The size of a motor unit is variable depending on the nature of the muscle. When more than one motor unit is activated in a muscle this is referred to as **motor unit recruitment**.

A small motor unit is an arrangement where a single motor neuron supplies a small number of muscle fibers in a muscle. Small motor units permit very fine motor control of the muscle. The best example in humans is the small motor units of the extraocular eye muscles that move the eyeballs. There are thousands of muscle fibers in each muscle, but every six or so fibers are supplied by a single motor neuron, as the axons branch to form synaptic connections at their individual NMJs. This allows for exquisite control of eye movements so that both eyes can quickly focus on the same object. Small motor units are also involved in the many fine movements of the fingers and thumb of the hand for grasping, texting, etc.

A large motor unit is an arrangement where a single motor neuron supplies a large number of muscle fibers in a muscle. Large motor units are concerned with simple, or "gross," movements, such as powerfully extending the knee joint. The best example is the large motor units of the thigh muscles or back muscles, where a single motor neuron will supply thousands of muscle fibers in a muscle, as its axon splits into thousands of branches.

There is a wide range of motor units within many skeletal muscles, which gives the nervous system a wide range of control over the muscle. The small motor units in the muscle will have smaller, lower-threshold motor neurons that are more excitable, firing first to their skeletal muscle fibers, which also tend to be the smallest. Activation of these smaller motor units,

results in a relatively small degree of contractile strength (tension) generated in the muscle. As more strength is needed, larger motor units, with bigger, higher-threshold motor neurons are enlisted to activate larger muscle fibers. This increasing activation of motor units produces an increase in muscle contraction known as the size principle. As more motor units are recruited, the muscle contraction grows progressively stronger. In some muscles, the largest motor units may generate a contractile force of 50 times more than the smallest motor units in the muscle. This allows a feather to be picked up using the biceps brachii arm muscle with minimal force, and a heavy weight to be lifted by the same muscle by recruiting the largest motor units.

When necessary, the maximal number of motor units in a muscle can be recruited simultaneously, producing the maximum force of contraction for that muscle, but this cannot last for very long because of the energy requirements to sustain the contraction. To prevent complete muscle fatigue, motor units are generally not all simultaneously active, but instead some motor units rest while others are active, which allows for longer muscle contractions. The nervous system uses recruitment as a mechanism to efficiently utilize a skeletal muscle.

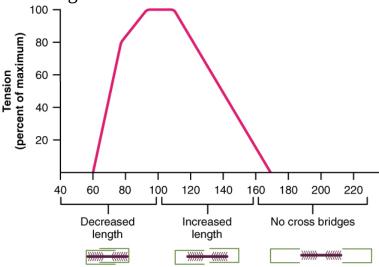
The Length-Tension Range of a Sarcomere

When a skeletal muscle fiber contracts, myosin heads attach to actin to form cross-bridges followed by the thin filaments sliding over the thick filaments as the heads pull the actin, and this results in sarcomere shortening, creating the tension of the muscle contraction. The cross-bridges can only form where thin and thick filaments already overlap, so that the length of the sarcomere has a direct influence on the force generated when the sarcomere shortens. This is called the length-tension relationship.

The ideal length of a sarcomere to produce maximal tension occurs at 80 percent to 120 percent of its resting length, with 100 percent being the state where the medial edges of the thin filaments are just at the most-medial myosin heads of the thick filaments ([link]). This length maximizes the overlap of actin-binding sites and myosin heads. If a sarcomere is stretched past this ideal length (beyond 120 percent), thick and thin filaments do not

overlap sufficiently, which results in less tension produced. If a sarcomere is shortened beyond 80 percent, the zone of overlap is reduced with the thin filaments jutting beyond the last of the myosin heads and shrinks the H zone, which is normally composed of myosin tails. Eventually, there is nowhere else for the thin filaments to go and the amount of tension is diminished. If the muscle is stretched to the point where thick and thin filaments do not overlap at all, no cross-bridges can be formed, and no tension is produced in that sarcomere. This amount of stretching does not usually occur, as accessory proteins and connective tissue oppose extreme stretching.

The Length-Tension Curve in a Muscle Fiber



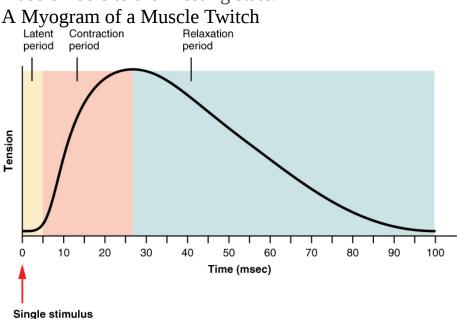
Percentage sarcomere length

Sarcomeres produce maximal tension when thick and thin filaments overlap between about 80 percent to 120 percent.

The Frequency of Motor Neuron Stimulation

A single action potential from a motor neuron will produce a single contraction in the muscle fibers of its motor unit. This isolated contraction is called a **twitch**. A twitch can last for a few milliseconds or 100 milliseconds, depending on the muscle type. The tension produced by a

single twitch can be measured by a **myogram**, an instrument that measures the amount of tension produced over time ([link]). Each twitch undergoes three phases. The first phase is the **latent period**, during which the action potential is being propagated along the sarcolemma and Ca⁺⁺ ions are released from the SR. This is the phase during which excitation and contraction are being coupled but contraction has yet to occur. The **contraction phase** occurs next. The Ca⁺⁺ ions in the sarcoplasm have bound to troponin, tropomyosin has shifted away from actin-binding sites, cross-bridges formed, and sarcomeres are actively shortening to the point of peak tension. The last phase is the **relaxation phase**, when tension decreases due to the cessation of the stimulus. Ca⁺⁺ ions are pumped out of the sarcoplasm into the SR, and cross-bridge cycling stops, returning the muscle fibers to their resting state.

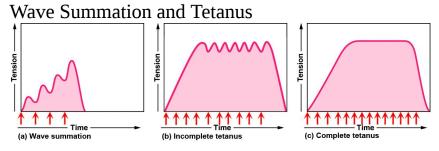


A single muscle twitch has a latent period, a contraction phase when tension increases, and a relaxation phase when tension decreases. During the latent period, the action potential is being propagated along the sarcolemma. During the contraction phase, Ca⁺⁺ ions in the sarcoplasm bind to troponin, tropomyosin moves from actin-binding sites, cross-bridges form, and sarcomeres shorten. During the relaxation phase, tension decreases as

Ca⁺⁺ ions are pumped out of the sarcoplasm and cross-bridge cycling stops.

Although a person can experience a muscle "twitch," a single twitch does not produce any significant muscle activity in a living body. A series of action potentials to the muscle fibers is necessary to produce a muscle contraction that can produce work. Normal muscle contraction is more sustained, and it can be modified by input from the nervous system to produce varying amounts of force; this is called a **graded muscle response**. The frequency of action potentials (nerve impulses) from a motor neuron and the number of motor neurons transmitting action potentials both affect the tension produced in skeletal muscle.

The rate at which a motor neuron fires action potentials affects the tension produced in the skeletal muscle. If the fibers are stimulated while a previous twitch is still occurring, the second twitch will be stronger. This response is called **wave summation**, because the excitation-contraction coupling effects of successive motor neuron signaling is summed, or added together ([link]a). At the molecular level, summation occurs because the second stimulus occurs before the relaxation phase is complete, leaving a higher concentration of calcium in the sarcoplasm. The second stimulus will then trigger the release of more Ca⁺⁺ ions, which become available to activate additional sarcomeres while the muscle is still contracting from the first stimulus. Summation results in greater contraction of the motor unit.



(a) The excitation-contraction coupling effects of successive motor neuron signaling is added together which is referred to as wave summation. The bottom of each wave, the end

of the relaxation phase, represents the point of stimulus. (b) When the stimulus frequency is so high that the relaxation phase disappears completely, the contractions become continuous; this is called tetanus. Red arrows equals stimulus applied.

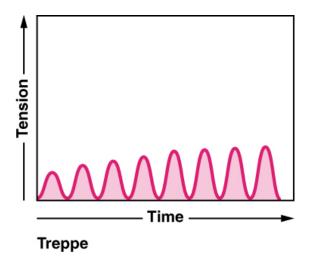
If the frequency of motor neuron signaling increases, summation and subsequent muscle tension in the motor unit continues to rise until it reaches a peak point. The tension at this point is about three to four times greater than the tension of a single twitch, a state referred to as incomplete tetanus. During incomplete tetanus, the muscle goes through quick cycles of contractions with a short relaxation phase for each. If the stimulus frequency is so high that the relaxation phase disappears completely, contractions become continuous in a process called complete **tetanus** ([link]b).

During complete tetanus, the concentration of Ca⁺⁺ ions in the sarcoplasm allows virtually all of the sarcomeres to form cross-bridges and shorten, so that a contraction can continue uninterrupted (until the muscle fatigues and can no longer produce tension).

Treppe

When a skeletal muscle has been dormant for an extended period and then activated to contract, with all other things being equal, the initial contractions generate about one-half the force of later contractions. The muscle tension increases in a graded manner that to some looks like a set of stairs. This tension increase is called **treppe**, a condition where muscle contractions become more efficient. It's also known as the "staircase effect" ([link]).

Treppe



When muscle tension increases in a graded manner that looks like a set of stairs, it is called treppe. The bottom of each wave represents the point of stimulus.

It is believed that treppe results from a higher concentration of Ca⁺⁺ in the sarcoplasm resulting from the steady stream of signals from the motor neuron. It can only be maintained with adequate ATP.

Fiber Diamter

The ability of a muscle fiber to generate force is dependent on the number of cross bridges that a muscle can form. If a muscle has more sarcomeres, more cross bridges can form and the muscle can generate more force than a muscle with fewer sarcomeres and therefore less cross bridge formation.

Muscle Tone

Skeletal muscles are rarely completely relaxed, or flaccid. Even if a muscle is not producing movement, it is contracted a small amount to maintain its contractile proteins and produce **muscle tone**. The tension produced by

muscle tone allows muscles to continually stabilize joints and maintain posture.

Muscle tone is accomplished by a complex interaction between the nervous system and skeletal muscles that results in the activation of a few motor units at a time, most likely in a cyclical manner. In this manner, muscles never fatigue completely, as some motor units can recover while others are active.

The absence of the low-level contractions that lead to muscle tone is referred to as **hypotonia** or atrophy, and can result from damage to parts of the central nervous system (CNS), such as the cerebellum, or from loss of innervations to a skeletal muscle, as in poliomyelitis. Hypotonic muscles have a flaccid appearance and display functional impairments, such as weak reflexes. Conversely, excessive muscle tone is referred to as **hypertonia**, accompanied by hyperreflexia (excessive reflex responses), often the result of damage to upper motor neurons in the CNS. Hypertonia can present with muscle rigidity (as seen in Parkinson's disease) or spasticity, a phasic change in muscle tone, where a limb will "snap" back from passive stretching (as seen in some strokes).

Chapter Review

The number of cross-bridges formed between actin and myosin determines the amount of tension produced by a muscle. The length of a sarcomere is optimal when the zone of overlap between thin and thick filaments is greatest. Muscles that are stretched or compressed too greatly do not produce maximal amounts of power. A motor unit is formed by a motor neuron and all of the muscle fibers that are innervated by that same motor neuron. A single contraction is called a twitch. A muscle twitch has a latent period, a contraction phase, and a relaxation phase. A graded muscle response allows variation in muscle tension. Summation occurs as successive stimuli are added together to produce a stronger muscle contraction. Tetanus is the fusion of contractions to produce a continuous contraction. Increasing the number of motor neurons involved increases the amount of motor units activated in a muscle, which is called recruitment.

Muscle tone is the constant low-level contractions that allow for posture and stability.

Glossary

concentric contraction

muscle contraction that shortens the muscle to move a load

contraction phase

twitch contraction phase when tension increases

eccentric contraction

muscle contraction that lengthens the muscle as the tension is diminished

graded muscle response

modification of contraction strength

hypertonia

abnormally high muscle tone

hypotonia

abnormally low muscle tone caused by the absence of low-level contractions

isometric contraction

muscle contraction that occurs with no change in muscle length

isotonic contraction

muscle contraction that involves changes in muscle length

latent period

the time when a twitch does not produce contraction

motor unit

motor neuron and the group of muscle fibers it innervates

motor unit recruitment

increase in the number of motor units involved in contraction

muscle tension

force generated by the contraction of the muscle; tension generated during isotonic contractions and isometric contractions

muscle tone

low levels of muscle contraction that occur when a muscle is not producing movement

myogram

instrument used to measure twitch tension

relaxation phase

period after twitch contraction when tension decreases

size principle

the correspondence between the size of motor units and the order of recruitment

tetanus

a continuous fused contraction

treppe

stepwise increase in contraction tension

twitch

single contraction produced by one action potential

wave summation

addition of successive neural stimuli to produce greater contraction

OU Human Physiology: Types of Muscle Fibers By the end of this section, you will be able to:

 Compare and contrast the structure, function, and metabolic pathways used by the three different muscle fiber types

Two criteria to consider when classifying the types of muscle fibers are how fast some fibers contract relative to others, and how fibers produce ATP. Using these criteria, there are three main types of skeletal muscle fibers. Slow oxidative (SO) fibers contract relatively slowly and use aerobic respiration (oxygen and glucose) to produce ATP. Fast oxidative (FO) fibers have fast contractions and primarily use aerobic respiration, but because they may switch to anaerobic respiration (glycolysis), can fatigue more quickly than SO fibers. Lastly, fast glycolytic (FG) fibers have fast contractions and primarily use anaerobic glycolysis. The FG fibers fatigue more quickly than the others. Most skeletal muscles in a human contain(s) all three types, although in varying proportions.

The speed of contraction is dependent on how quickly myosin's ATPase hydrolyzes ATP to produce cross-bridge action. Fast fibers hydrolyze ATP approximately twice as quickly as slow fibers, resulting in much quicker cross-bridge cycling (which pulls the thin filaments toward the center of the sarcomeres at a faster rate). The primary metabolic pathway used by a muscle fiber determines whether the fiber is classified as oxidative or glycolytic. If a fiber primarily produces ATP through aerobic pathways it is oxidative. More ATP can be produced during each metabolic cycle, making the fiber more resistant to fatigue. Glycolytic fibers primarily create ATP through anaerobic glycolysis, which produces less ATP per cycle. As a result, glycolytic fibers fatigue at a quicker rate.

The oxidative fibers contain many more mitochondria than the glycolytic fibers, because aerobic metabolism, which uses oxygen (O_2) in the metabolic pathway, occurs in the mitochondria. The SO fibers possess a large number of mitochondria and are capable of contracting for longer periods because of the large amount of ATP they can produce, but they have a relatively small diameter and do not produce a large amount of tension. SO fibers are extensively supplied with blood capillaries to supply O_2 from the red blood cells in the bloodstream. The SO fibers also possess

myoglobin, an O_2 -carrying molecule similar to O_2 -carrying hemoglobin in the red blood cells. The myoglobin stores some of the needed O_2 within the fibers themselves (and gives SO fibers their red color). All of these features allow SO fibers to produce large quantities of ATP, which can sustain muscle activity without fatiguing for long periods of time.

The fact that SO fibers can function for long periods without fatiguing makes them useful in maintaining posture, producing isometric contractions, stabilizing bones and joints, and making small movements that happen often but do not require large amounts of energy. They do not produce high tension, and thus they are not used for powerful, fast movements that require high amounts of energy and rapid cross-bridge cycling.

FO fibers are sometimes called intermediate fibers because they possess characteristics that are intermediate between fast fibers and slow fibers. They produce ATP relatively quickly, more quickly than SO fibers, and thus can produce relatively high amounts of tension. They are oxidative because they produce ATP aerobically, possess high amounts of mitochondria, and do not fatigue quickly. However, FO fibers do not possess significant myoglobin, giving them a lighter color than the red SO fibers. FO fibers are used primarily for movements, such as walking, that require more energy than postural control but less energy than an explosive movement, such as sprinting. FO fibers are useful for this type of movement because they produce more tension than SO fibers but they are more fatigue-resistant than FG fibers.

FG fibers primarily use anaerobic glycolysis as their ATP source. They have a large diameter and possess high amounts of glycogen, which is used in glycolysis to generate ATP quickly to produce high levels of tension. Because they do not primarily use aerobic metabolism, they do not possess substantial numbers of mitochondria or significant amounts of myoglobin and therefore have a white color. FG fibers are used to produce rapid, forceful contractions to make quick, powerful movements. These fibers fatigue quickly, permitting them to only be used for short periods. Most muscles possess a mixture of each fiber type. The predominant fiber type in a muscle is determined by the primary function of the muscle.

Chapter Review

ATP provides the energy for muscle contraction. The three mechanisms for ATP regeneration are creatine phosphate, anaerobic glycolysis, and aerobic metabolism. Creatine phosphate provides about the first 15 seconds of ATP at the beginning of muscle contraction. Anaerobic glycolysis produces small amounts of ATP in the absence of oxygen for a short period. Aerobic metabolism utilizes oxygen to produce much more ATP, allowing a muscle to work for longer periods. Muscle fatigue, which has many contributing factors, occurs when muscle can no longer contract. An oxygen debt is created as a result of muscle use. The three types of muscle fiber are slow oxidative (SO), fast oxidative (FO) and fast glycolytic (FG). SO fibers use aerobic metabolism to produce low power contractions over long periods and are slow to fatigue. FO fibers use aerobic metabolism to produce ATP but produce higher tension contractions than SO fibers. FG fibers use anaerobic metabolism to produce powerful, high-tension contractions but fatigue quickly.

Glossary

fast glycolytic (FG) muscle fiber that primarily uses anaerobic glycolysis

fast oxidative (FO) intermediate muscle fiber that is between slow oxidative and fast glycolytic fibers

slow oxidative (SO) muscle fiber that primarily uses aerobic respiration

OU Human Physiology: Exercise and Muscle Performance

Physical training alters the appearance of skeletal muscles and can produce changes in muscle performance. Conversely, a lack of use can result in decreased performance and muscle appearance. Although muscle cells can change in size, new cells are not formed when muscles grow. Instead, structural proteins are added to muscle fibers in a process called **hypertrophy**, so cell diameter increases. The reverse, when structural proteins are lost and muscle mass decreases, is called **atrophy**. Age-related muscle atrophy is called **sarcopenia**. Cellular components of muscles can also undergo changes in response to changes in muscle use.

Endurance Exercise

Slow fibers are predominantly used in endurance exercises that require little force but involve numerous repetitions. The aerobic metabolism used by slow-twitch fibers allows them to maintain contractions over long periods. Endurance training modifies these slow fibers to make them even more efficient by producing more mitochondria to enable more aerobic metabolism and more ATP production. Endurance exercise can also increase the amount of myoglobin in a cell, as increased aerobic respiration increases the need for oxygen. Myoglobin is found in the sarcoplasm and acts as an oxygen storage supply for the mitochondria.

The training can trigger the formation of more extensive capillary networks around the fiber, a process called **angiogenesis**, to supply oxygen and remove metabolic waste. To allow these capillary networks to supply the deep portions of the muscle, muscle mass does not greatly increase in order to maintain a smaller area for the diffusion of nutrients and gases. All of these cellular changes result in the ability to sustain low levels of muscle contractions for greater periods without fatiguing.

The proportion of SO muscle fibers in muscle determines the suitability of that muscle for endurance, and may benefit those participating in endurance activities. Postural muscles have a large number of SO fibers and relatively few FO and FG fibers, to keep the back straight ([link]). Endurance athletes, like marathon-runners also would benefit from a larger proportion of SO

fibers, but it is unclear if the most-successful marathoners are those with naturally high numbers of SO fibers, or whether the most successful marathon runners develop high numbers of SO fibers with repetitive training. Endurance training can result in overuse injuries such as stress fractures and joint and tendon inflammation.

Marathoners



Long-distance runners have a large number of SO fibers and relatively few FO and FG fibers. (credit: "Tseo2"/Wikimedia Commons)

Resistance Exercise

Resistance exercises, as opposed to endurance exercise, require large amounts of FG fibers to produce short, powerful movements that are not repeated over long periods. The high rates of ATP hydrolysis and crossbridge formation in FG fibers result in powerful muscle contractions. Muscles used for power have a higher ratio of FG to SO/FO fibers, and trained athletes possess even higher levels of FG fibers in their muscles. Resistance exercise affects muscles by increasing the formation of myofibrils, thereby increasing the thickness of muscle fibers. This added structure causes hypertrophy, or the enlargement of muscles, exemplified by

the large skeletal muscles seen in body builders and other athletes ([link]). Because this muscular enlargement is achieved by the addition of structural proteins, athletes trying to build muscle mass often ingest large amounts of protein.

Hypertrophy



Body builders have a large number of FG fibers and relatively few FO and SO fibers. (credit: Lin Mei/flickr)

Except for the hypertrophy that follows an increase in the number of sarcomeres and myofibrils in a skeletal muscle, the cellular changes observed during endurance training do not usually occur with resistance training. There is usually no significant increase in mitochondria or capillary density. However, resistance training does increase the development of connective tissue, which adds to the overall mass of the muscle and helps to contain muscles as they produce increasingly powerful contractions. Tendons also become stronger to prevent tendon damage, as the force produced by muscles is transferred to tendons that attach the muscle to bone.

For effective strength training, the intensity of the exercise must continually be increased. For instance, continued weight lifting without increasing the weight of the load does not increase muscle size. To produce ever-greater results, the weights lifted must become increasingly heavier, making it more

difficult for muscles to move the load. The muscle then adapts to this heavier load, and an even heavier load must be used if even greater muscle mass is desired.

If done improperly, resistance training can lead to overuse injuries of the muscle, tendon, or bone. These injuries can occur if the load is too heavy or if the muscles are not given sufficient time between workouts to recover or if joints are not aligned properly during the exercises. Cellular damage to muscle fibers that occurs after intense exercise includes damage to the sarcolemma and myofibrils. This muscle damage contributes to the feeling of soreness after strenuous exercise, but muscles gain mass as this damage is repaired, and additional structural proteins are added to replace the damaged ones. Overworking skeletal muscles can also lead to tendon damage and even skeletal damage if the load is too great for the muscles to bear.

Performance-Enhancing Substances

Some athletes attempt to boost their performance by using various agents that may enhance muscle performance. Anabolic steroids are one of the more widely known agents used to boost muscle mass and increase power output. Anabolic steroids are a form of testosterone, a male sex hormone that stimulates muscle formation, leading to increased muscle mass.

Endurance athletes may also try to boost the availability of oxygen to muscles to increase aerobic respiration by using substances such as erythropoietin (EPO), a hormone normally produced in the kidneys, which triggers the production of red blood cells. The extra oxygen carried by these blood cells can then be used by muscles for aerobic respiration. Human growth hormone (hGH) is another supplement, and although it can facilitate building muscle mass, its main role is to promote the healing of muscle and other tissues after strenuous exercise. Increased hGH may allow for faster recovery after muscle damage, reducing the rest required after exercise, and allowing for more sustained high-level performance.

Although performance-enhancing substances often do improve performance, most are banned by governing bodies in sports and are illegal

for nonmedical purposes. Their use to enhance performance raises ethical issues of cheating because they give users an unfair advantage over nonusers. A greater concern, however, is that their use carries serious health risks. The side effects of these substances are often significant, nonreversible, and in some cases fatal. The physiological strain caused by these substances is often greater than what the body can handle, leading to effects that are unpredictable and dangerous. Anabolic steroid use has been linked to infertility, aggressive behavior, cardiovascular disease, and brain cancer.

Similarly, some athletes have used creatine to increase power output. Creatine phosphate provides quick bursts of ATP to muscles in the initial stages of contraction. Increasing the amount of creatine available to cells is thought to produce more ATP and therefore increase explosive power output, although its effectiveness as a supplement has been questioned.

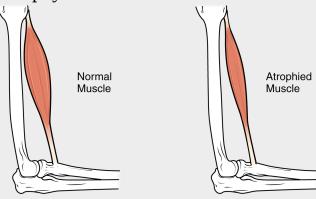
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Everyday Connection Aging and Muscle Tissue

Although atrophy due to disuse can often be reversed with exercise, muscle atrophy with age, referred to as sarcopenia, is irreversible. This is a primary reason why even highly trained athletes succumb to declining performance with age. This decline is noticeable in athletes whose sports require strength and powerful movements, such as sprinting, whereas the effects of age are less noticeable in endurance athletes such as marathon runners or long-distance cyclists. As muscles age, muscle fibers die, and they are replaced by connective tissue and adipose tissue ([link]). Because those tissues cannot contract and generate force as muscle can, muscles lose the ability to produce powerful contractions. The decline in muscle mass causes a loss of strength, including the strength required for posture and mobility. This may be caused by a reduction in FG fibers that hydrolyze ATP quickly to produce short, powerful contractions. Muscles in older people sometimes possess greater numbers of SO fibers, which are responsible for longer contractions and do not produce powerful movements. There may also be a reduction in the size of motor units,

resulting in fewer fibers being stimulated and less muscle tension being produced.





Muscle mass is reduced as muscles atrophy with disuse.

Sarcopenia can be delayed to some extent by exercise, as training adds structural proteins and causes cellular changes that can offset the effects of atrophy. Increased exercise can produce greater numbers of cellular mitochondria, increase capillary density, and increase the mass and strength of connective tissue. The effects of age-related atrophy are especially pronounced in people who are sedentary, as the loss of muscle cells is displayed as functional impairments such as trouble with locomotion, balance, and posture. This can lead to a decrease in quality of life and medical problems, such as joint problems because the muscles that stabilize bones and joints are weakened. Problems with locomotion and balance can also cause various injuries due to falls.

Chapter Review

Hypertrophy is an increase in muscle mass due to the addition of structural proteins. The opposite of hypertrophy is atrophy, the loss of muscle mass due to the breakdown of structural proteins. Endurance exercise causes an increase in cellular mitochondria, myoglobin, and capillary networks in SO fibers. Endurance athletes have a high level of SO fibers relative to the

other fiber types. Resistance exercise causes hypertrophy. Power-producing muscles have a higher number of FG fibers than of slow fibers. Strenuous exercise causes muscle cell damage that requires time to heal. Some athletes use performance-enhancing substances to enhance muscle performance. Muscle atrophy due to age is called sarcopenia and occurs as muscle fibers die and are replaced by connective and adipose tissue.

Glossary

angiogenesis

formation of blood capillary networks

atrophy

loss of structural proteins from muscle fibers

hypertrophy

addition of structural proteins to muscle fibers

sarcopenia

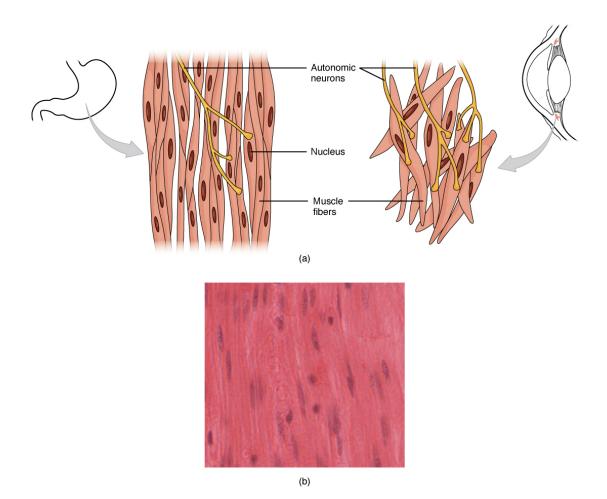
age-related muscle atrophy

OU Human Physiology: Smooth Muscle By the end of this section, you will be able to:

- Describe a dense body in smooth muscle cells
- Describe excitation contraction coupling in smooth muscle
- Describe the process of smooth muscle relaxation
- List the efferent branch of the nervous system involved in regulation of skeletal, smooth, and cardiac muscle
- Compare and contrast multi-unit and single-unit smooth muscle

Smooth muscle (so-named because the cells do not have striations) is present in the walls of hollow organs like the urinary bladder, uterus, stomach, intestines, and in the walls of passageways, such as the arteries and veins of the circulatory system, and the tracts of the respiratory, urinary, and reproductive systems ([link]a,b). Smooth muscle is also present in the eyes, where it functions to change the size of the iris and alter the shape of the lens; and in the skin where it causes hair to stand erect in response to cold temperature or fear.

Smooth Muscle Tissue



Smooth muscle tissue is found around organs in the digestive, respiratory, reproductive tracts and the iris of the eye. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:

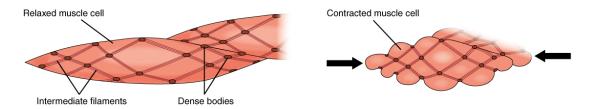


View the University of Michigan WebScope at http://virtualslides.med.umich.edu/Histology/Digestive%20System/Intestines/169 HISTO 40X.svs/view.apml to explore the tissue sample in greater detail.

Smooth muscle fibers are spindle-shaped (wide in the middle and tapered at both ends, somewhat like a football) and have a single nucleus; they range from about 30 to 200 μ m (thousands of times shorter than skeletal muscle fibers), and they produce their own connective tissue, endomysium. Although they do not have striations and sarcomeres, smooth muscle fibers do have actin and myosin contractile proteins, and thick and thin filaments. These thin filaments are anchored by dense bodies. A **dense body** is analogous to the Z-discs of skeletal and cardiac muscle fibers and is fastened to the sarcolemma. Calcium ions are supplied by the SR in the fibers and by sequestration from the extracellular fluid through membrane indentations called calveoli.

Because smooth muscle cells do not contain troponin, cross-bridge formation is not regulated by the troponin-tropomyosin complex but instead by the regulatory protein calmodulin. In a smooth muscle fiber, external Ca⁺⁺ ions passing through opened calcium channels in the sarcolemma, and additional Ca⁺⁺ released from SR, bind to calmodulin. The Ca⁺⁺calmodulin complex then activates an enzyme called myosin (light chain) kinase, which, in turn, activates the myosin heads by phosphorylating them (converting ATP to ADP and P_i, with the P_i attaching to the head). The heads can then attach to actin-binding sites and pull on the thin filaments. The thin filaments also are anchored to the dense bodies; the structures invested in the inner membrane of the sarcolemma (desmosomes junctions) that also have cord-like intermediate filaments attached to them. When the thin filaments slide past the thick filaments, they pull on the dense bodies, structures tethered to the sarcolemma, which then pull on the intermediate filaments networks throughout the sarcoplasm. This arrangement causes the entire muscle fiber to contract in a manner whereby the ends are pulled toward the center, causing the midsection to bulge in a corkscrew motion ([<u>link</u>]).

Muscle Contraction



The dense bodies and intermediate filaments are networked through the sarcoplasm, which cause the muscle fiber to contract.

Although smooth muscle contraction relies on the presence of Ca⁺⁺ ions, smooth muscle fibers have a much smaller diameter than skeletal muscle cells. T-tubules are not required to reach the interior of the cell and therefore not necessary to transmit an action potential deep into the fiber. Smooth muscle fibers have a limited calcium-storing SR but have calcium channels in the sarcolemma (similar to cardiac muscle fibers) that open during the action potential along the sarcolemma. The influx of extracellular Ca⁺⁺ ions, which diffuse into the sarcoplasm to reach the calmodulin, accounts for most of the Ca⁺⁺ that triggers contraction of a smooth muscle cell.

Muscle contraction continues until ATP-dependent calcium pumps actively transport Ca-ions back into the SR and extracellular fluid. Ca-ATPase pumps are on the SR and sarcolemma while Ca-Na countertransport pump is on the sarcolemma. A low concentration of calcium remains in the sarcoplasm to maintain muscle tone. This remaining calcium keeps the muscle slightly contracted, which is important in certain tracts and around blood vessels.

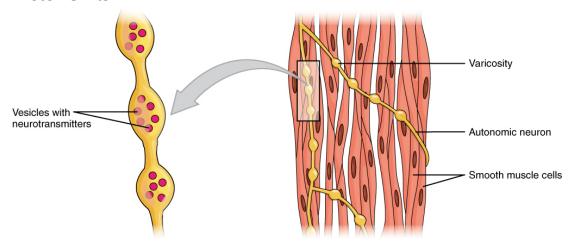
Because most smooth muscles must function for long periods without rest, their power output is relatively low, but contractions can continue without using large amounts of energy. Some smooth muscle can also maintain contractions even as Ca⁺⁺ is removed and myosin kinase is inactivated/dephosphorylated. This can happen as a subset of cross-bridges

between myosin heads and actin, called **latch-bridges**, keep the thick and thin filaments linked together for a prolonged period, and without the need for ATP. This allows for the maintaining of muscle "tone" in smooth muscle that lines arterioles and other visceral organs with very little energy expenditure.

Smooth muscle is not under voluntary control; thus, it is called involuntary muscle. The triggers for smooth muscle contraction include hormones, neural stimulation by the ANS, and local factors. In certain locations, such as the walls of visceral organs, stretching the muscle can trigger its contraction (the stretch-relaxation response).

Axons of neurons in the ANS do not form the highly organized NMJs with smooth muscle, as seen between motor neurons and skeletal muscle fibers. Instead, there is a series of neurotransmitter-filled bulges called varicosities as an axon courses through smooth muscle, loosely forming motor units ([link]). A varicosity releases neurotransmitters into the synaptic cleft. Also, visceral muscle in the walls of the hollow organs (except the heart) contains pacesetter cells. A pacesetter cell can spontaneously trigger action potentials and contractions in the muscle.

Motor Units



A series of axon-like swelling, called varicosities or "boutons," from autonomic neurons form motor units through the smooth muscle.

Smooth muscle is organized in two ways: as single-unit smooth muscle, which is much more common; and as multiunit smooth muscle. The two types have different locations in the body and have different characteristics. Single-unit muscle has its muscle fibers joined by gap junctions so that the muscle contracts as a single unit. This type of smooth muscle is found in the walls of all visceral organs except the heart (which has cardiac muscle in its walls), and so it is commonly called **visceral muscle**. Because the muscle fibers are not constrained by the organization and stretchability limits of sarcomeres, visceral smooth muscle has a **stress-relaxation response**. This means that as the muscle of a hollow organ is stretched when it fills, the mechanical stress of the stretching will trigger contraction, but this is immediately followed by relaxation so that the organ does not empty its contents prematurely. This is important for hollow organs, such as the stomach or urinary bladder, which continuously expand as they fill. The smooth muscle around these organs also can maintain a muscle tone when the organ empties and shrinks, a feature that prevents "flabbiness" in the empty organ. In general, visceral smooth muscle produces slow, steady contractions that allow substances, such as food in the digestive tract, to move through the body.

Multiunit smooth muscle cells rarely possess gap junctions, and thus are not electrically coupled. As a result, contraction does not spread from one cell to the next, but is instead confined to the cell that was originally stimulated. Stimuli for multiunit smooth muscles come from autonomic nerves or hormones but not from stretching. This type of tissue is found around large blood vessels, in the respiratory airways, and in the eyes.

Hyperplasia in Smooth Muscle

Similar to skeletal and cardiac muscle cells, smooth muscle can undergo hypertrophy to increase in size. Unlike other muscle, smooth muscle can also divide to produce more cells, a process called **hyperplasia**. This can most evidently be observed in the uterus at puberty, which responds to increased estrogen levels by producing more uterine smooth muscle fibers, and greatly increases the size of the myometrium.

Chapter Review

Smooth muscle is found throughout the body around various organs and tracts. Smooth muscle cells have a single nucleus, and are spindle-shaped. Smooth muscle cells can undergo hyperplasia, mitotically dividing to produce new cells. The smooth cells are nonstriated, but their sarcoplasm is filled with actin and myosin, along with dense bodies in the sarcolemma to anchor the thin filaments and a network of intermediate filaments involved in pulling the sarcolemma toward the fiber's middle, shortening it in the process. Ca++ ions trigger contraction when they are released from SR and enter through opened voltage-gated calcium channels. Smooth muscle contraction is initiated when the Ca++ binds to intracellular calmodulin. which then activates an enzyme called myosin kinase that phosphorylates myosin heads so they can form the cross-bridges with actin and then pull on the thin filaments. Smooth muscle can be stimulated by pacesetter cells, by the autonomic nervous system, by hormones, spontaneously, or by stretching. The fibers in some smooth muscle have latch-bridges, crossbridges that cycle slowly without the need for ATP; these muscles can maintain low-level contractions for long periods. Single-unit smooth muscle tissue contains gap junctions to synchronize membrane depolarization and contractions so that the muscle contracts as a single unit. Single-unit smooth muscle in the walls of the viscera, called visceral muscle, has a stress-relaxation response that permits muscle to stretch, contract, and relax as the organ expands. Multiunit smooth muscle cells do not possess gap junctions, and contraction does not spread from one cell to the next.

Glossary

calmodulin

regulatory protein that facilitates contraction in smooth muscles

dense body

sarcoplasmic structure that attaches to the sarcolemma and shortens the muscle as thin filaments slide past thick filaments

hyperplasia

process in which one cell splits to produce new cells

latch-bridges

subset of a cross-bridge in which actin and myosin remain locked together

pacesetter cell

cell that triggers action potentials in smooth muscle

stress-relaxation response

relaxation of smooth muscle tissue after being stretched

varicosity

enlargement of neurons that release neurotransmitters into synaptic clefts

visceral muscle

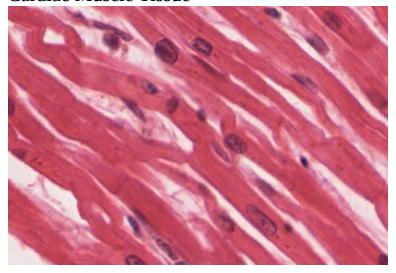
smooth muscle found in the walls of visceral organs

OU Human Physiology: Cardiac Muscle Tissue By the end of this section, you will be able to:

• Differentiate between a pacemaker potential and a slow wave potential and whether myogenic or neurogenic muscle fibers generate these potentials

Cardiac muscle tissue is only found in the heart. Highly coordinated contractions of cardiac muscle pump blood into the vessels of the circulatory system. Similar to skeletal muscle, cardiac muscle is striated and organized into sarcomeres, possessing the same banding organization as skeletal muscle ([link]). However, cardiac muscle fibers are shorter than skeletal muscle fibers and usually contain only one nucleus, which is located in the central region of the cell. Cardiac muscle fibers also possess many mitochondria and myoglobin, as ATP is produced primarily through aerobic metabolism. Cardiac muscle fibers cells also are extensively branched and are connected to one another at their ends by intercalated discs. An **intercalated disc** allows the cardiac muscle cells to contract in a wave-like pattern so that the heart can work as a pump.

Cardiac Muscle Tissue



Cardiac muscle tissue is only found in the heart. LM × 1600. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

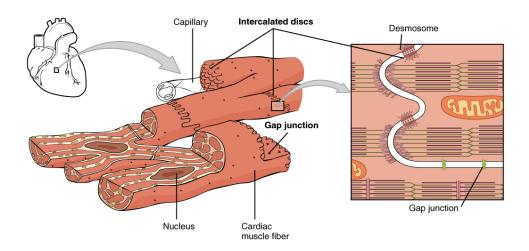
Note:



View the University of Michigan WebScope at http://virtualslides.med.umich.edu/Histology/Cardiovascular%20System/3 05 HISTO 40X.svs/view.apml to explore the tissue sample in greater detail.

Intercalated discs are part of the sarcolemma and contain two structures important in cardiac muscle contraction: gap junctions and desmosomes. A gap junction forms channels between adjacent cardiac muscle fibers that allow the depolarizing current produced by cations to flow from one cardiac muscle cell to the next. This joining is called electric coupling, and in cardiac muscle it allows the quick transmission of action potentials and the coordinated contraction of the entire heart. This network of electrically connected cardiac muscle cells creates a functional unit of contraction called a syncytium. The remainder of the intercalated disc is composed of desmosomes. A **desmosome** is a cell structure that anchors the ends of cardiac muscle fibers together so the cells do not pull apart during the stress of individual fibers contracting ([link]).

Cardiac Muscle



Intercalated discs are part of the cardiac muscle sarcolemma and they contain gap junctions and desmosomes.

Heart rate is controlled by specialized cardiac muscle cells called pacemaker cells. Although cardiac muscle cannot be consciously controlled, the pacemaker cells respond to signals from the autonomic nervous system (ANS) to speed up or slow down the heart rate. The pacemaker cells can also respond to various hormones that modulate heart rate to control blood pressure.

The wave of contraction that allows the heart to work as a unit, called a functional syncytium, begins with the pacemaker cells. This group of cells is self-excitable and able to depolarize to threshold and fire action potentials on their own, a feature called **autorhythmicity**; they do this at set intervals which determine heart rate. Because they are connected with gap junctions to surrounding muscle fibers and the specialized fibers of the heart's conduction system, the pacemaker cells are able to transfer the depolarization to the other cardiac muscle fibers in a manner that allows the heart to contract in a coordinated manner.

Another feature of cardiac muscle is its relatively long action potentials in its fibers, having a sustained depolarization "plateau." The plateau is produced by Ca⁺⁺ entry though voltage-gated calcium channels in the

sarcolemma of cardiac muscle fibers. This sustained depolarization (and Ca⁺⁺ entry) provides for a longer contraction than is produced by an action potential in skeletal muscle. Unlike skeletal muscle, a large percentage of the Ca⁺⁺ that initiates contraction in cardiac muscles comes from outside the cell rather than from the SR.

Chapter Review

Cardiac muscle is striated muscle that is present only in the heart. Cardiac muscle fibers have a single nucleus, are branched, and joined to one another by intercalated discs that contain gap junctions for depolarization between cells and desmosomes to hold the fibers together when the heart contracts. Contraction in each cardiac muscle fiber is triggered by Ca⁺⁺ ions in a similar manner as skeletal muscle, but here the Ca⁺⁺ ions come from SR and through voltage-gated calcium channels in the sarcolemma. Pacemaker cells stimulate the spontaneous contraction of cardiac muscle as a functional unit, called a syncytium.

Glossary

autorhythmicity

heart's ability to control its own contractions

desmosome

cell structure that anchors the ends of cardiac muscle fibers to allow contraction to occur

intercalated disc

part of the sarcolemma that connects cardiac tissue, and contains gap junctions and desmosomes

OU Human Physiology: Development and Regeneration of Muscle Tissue

Most muscle tissue of the body arises from embryonic mesoderm. Paraxial mesodermal cells adjacent to the neural tube form blocks of cells called **somites**. Skeletal muscles, excluding those of the head and limbs, develop from mesodermal somites, whereas skeletal muscle in the head and limbs develop from general mesoderm. Somites give rise to myoblasts. A **myoblast** is a muscle-forming stem cell that migrates to different regions in the body and then fuse(s) to form a syncytium, or **myotube**. As a myotube is formed from many different myoblast cells, it contains many nuclei, but has a continuous cytoplasm. This is why skeletal muscle cells are multinucleate, as the nucleus of each contributing myoblast remains intact in the mature skeletal muscle cell. However, cardiac and smooth muscle cells are not multinucleate because the myoblasts that form their cells do not fuse.

Gap junctions develop in the cardiac and single-unit smooth muscle in the early stages of development. In skeletal muscles, ACh receptors are initially present along most of the surface of the myoblasts, but spinal nerve innervation causes the release of growth factors that stimulate the formation of motor end-plates and NMJs. As neurons become active, electrical signals that are sent through the muscle influence the distribution of slow and fast fibers in the muscle.

Although the number of muscle cells is set during development, satellite cells help to repair skeletal muscle cells. A **satellite cell** is similar to a myoblast because it is a type of stem cell; however, satellite cells are incorporated into muscle cells and facilitate the protein synthesis required for repair and growth. These cells are located outside the sarcolemma and are stimulated to grow and fuse with muscle cells by growth factors that are released by muscle fibers under certain forms of stress. Satellite cells can regenerate muscle fibers to a very limited extent, but they primarily help to repair damage in living cells. If a cell is damaged to a greater extent than can be repaired by satellite cells, the muscle fibers are replaced by scar tissue in a process called **fibrosis**. Because scar tissue cannot contract, muscle that has sustained significant damage loses strength and cannot

produce the same amount of power or endurance as it could before being damaged.

Smooth muscle tissue can regenerate from a type of stem cell called a **pericyte**, which is found in some small blood vessels. Pericytes allow smooth muscle cells to regenerate and repair much more readily than skeletal and cardiac muscle tissue. Similar to skeletal muscle tissue, cardiac muscle does not regenerate to a great extent. Dead cardiac muscle tissue is replaced by scar tissue, which cannot contract. As scar tissue accumulates, the heart loses its ability to pump because of the loss of contractile power. However, some minor regeneration may occur due to stem cells found in the blood that occasionally enter cardiac tissue.

Note:

Career Connections

Physical Therapist

As muscle cells die, they are not regenerated but instead are replaced by connective tissue and adipose tissue, which do not possess the contractile abilities of muscle tissue. Muscles atrophy when they are not used, and over time if atrophy is prolonged, muscle cells die. It is therefore important that those who are susceptible to muscle atrophy exercise to maintain muscle function and prevent the complete loss of muscle tissue. In extreme cases, when movement is not possible, electrical stimulation can be introduced to a muscle from an external source. This acts as a substitute for endogenous neural stimulation, stimulating the muscle to contract and preventing the loss of proteins that occurs with a lack of use. Physiotherapists work with patients to maintain muscles. They are trained to target muscles susceptible to atrophy, and to prescribe and monitor exercises designed to stimulate those muscles. There are various causes of atrophy, including mechanical injury, disease, and age. After breaking a limb or undergoing surgery, muscle use is impaired and can lead to disuse atrophy. If the muscles are not exercised, this atrophy can lead to long-term muscle weakness. A stroke can also cause muscle impairment by interrupting neural stimulation to certain muscles. Without neural inputs, these muscles do not contract and thus begin to lose structural proteins.

Exercising these muscles can help to restore muscle function and minimize functional impairments. Age-related muscle loss is also a target of physical therapy, as exercise can reduce the effects of age-related atrophy and improve muscle function.

The goal of a physiotherapist is to improve physical functioning and reduce functional impairments; this is achieved by understanding the cause of muscle impairment and assessing the capabilities of a patient, after which a program to enhance these capabilities is designed. Some factors that are assessed include strength, balance, and endurance, which are continually monitored as exercises are introduced to track improvements in muscle function. Physiotherapists can also instruct patients on the proper use of equipment, such as crutches, and assess whether someone has sufficient strength to use the equipment and when they can function without it.

Chapter Review

Muscle tissue arises from embryonic mesoderm. Somites give rise to myoblasts and fuse to form a myotube. The nucleus of each contributing myoblast remains intact in the mature skeletal muscle cell, resulting in a mature, multinucleate cell. Satellite cells help to repair skeletal muscle cells. Smooth muscle tissue can regenerate from stem cells called pericytes, whereas dead cardiac muscle tissue is replaced by scar tissue. Aging causes muscle mass to decrease and be replaced by noncontractile connective tissue and adipose tissue.

Glossary

fibrosis
replacement of muscle fibers by scar tissue
myoblast
muscle-forming stem cell

myotube

fusion of many myoblast cells

pericyte

stem cell that regenerates smooth muscle cells

satellite cell

stem cell that helps to repair muscle cells

somites

blocks of paraxial mesoderm cells

OU Human Physiology: Respiratory System Introduction class="introduction" Mountain Climbers

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The thin air at high elevations can strain the human respiratory system. (credit: "bortescristian"/flickr.com
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Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Explain the location and function of the structures that make up the respiratory system
- Describe the forces that allow for air movement into and out of the lungs
- Explain the mechanisms for gas exchange
- Summarize the process of oxygen and carbon dioxide transport within the respiratory system
- Compare and contrast the respiratory volumes and capacities
- Explain the relevance of pulmonary function tests using a spirometer
- Create a flow chart illustrating how respiration is controlled
- Discuss how the respiratory system responds to exercise

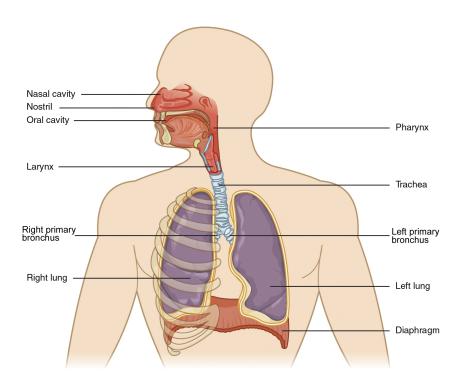
Hold your breath. Really! See how long you can hold your breath as you continue reading...How long can you do it? Chances are you are feeling uncomfortable already. A typical human cannot survive without breathing for more than 3 minutes, and even if you wanted to hold your breath longer, your autonomic nervous system would take control. This is because every cell in the body needs to run the oxidative stages of cellular respiration, the process by which energy is produced in the form of adenosine triphosphate (ATP). For oxidative phosphorylation to occur, oxygen is used as a reactant and carbon dioxide is released as a waste product. You may be surprised to learn that although oxygen is a critical need for cells, it is actually the accumulation of carbon dioxide that primarily drives your need to breathe. Carbon dioxide is exhaled and oxygen is inhaled through the respiratory system, which includes muscles to move air into and out of the lungs, passageways through which air moves, and microscopic gas exchange surfaces covered by capillaries. The circulatory system transports gases from the lungs to tissues throughout the body and vice versa. A variety of diseases can affect the respiratory system, such as asthma, emphysema, chronic obstruction pulmonary disorder (COPD), and lung cancer. All of these conditions affect the gas exchange process and result in labored breathing and other difficulties.

OU Human Physiology: Organs and Structures of the Respiratory System By the end of this section, you will be able to:

- Explain the location and function of the structures that make up the respiratory system
- Compare and contrast the functions of the conducting zone and respiratory zone
- Categorize the structures of the respiratory system into either the conducting zone or the respiratory zone
- Describe how the diameter, cilia and goblet cell concentration, and the amount of smooth muscle and cartilage changes throughout the conducting zone and respiratory zone
- Describe the function and importance of the three cell types found in the alveoli
- Explain how the respiratory membrane enhances gas exchange

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing ([link]).

Major Respiratory Structures



The major respiratory structures span the nasal cavity to the diaphragm.

Functionally, the respiratory system can be divided into a conducting zone and a respiratory zone. The **conducting zone** of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the **respiratory zone**.

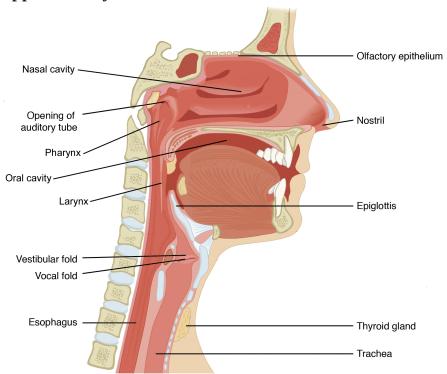
Conducting Zone

The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. The following structures are part of the conducting zone and carry out the functions of the conducting zone: larynx, trachea, primary bronchi, secondary bronchi, and bronchioles. Several of these structures perform other functions as well.

Nasal Cavity

The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose. Here we will only focus on the nasal cavity.

Upper Airway

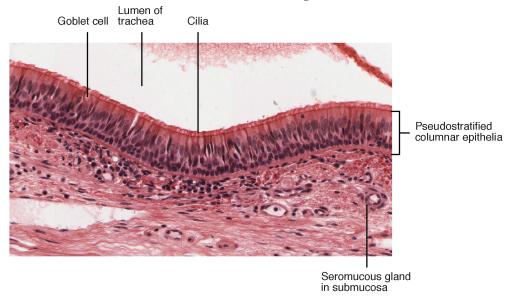


The anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odors is found deeper in the nasal cavity.

Most of the nasal cavity is lined by the **respiratory epithelium**. This epithelium is composed of pseudostratified ciliated columnar epithelium ([link]). The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris from the nasal cavity with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny

nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.

Pseudostratified Ciliated Columnar Epithelium



Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM × 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:			



View the University of Michigan WebScope at http://141.214.65.171/Histology/Basic%20Tissues/Epithelium%20and%20 CT/040 HISTO 40X.svs/view.apml? to explore the tissue sample in greater detail.

Pharynx

The **pharynx** is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities (see [link]). The pharynx is essentially the back of the throat.

Larynx

The **larynx** is a cartilaginous structure that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs (see [<u>link</u>]). Structures associated with the larynx also prevent food from entering the respiratory tract.

The **epiglottis** is a very flexible piece of elastic cartilage that covers the opening of the trachea (see [link]). When in the "closed" position, the unattached end of the epiglottis rests on the glottis. The **glottis** is the opening of the larynx. It is composed of the true vocal cords (see [link]). The act of swallowing causes the pharynx and larynx to lift upward, allowing the pharynx to expand and the epiglottis of the larynx to swing downward, closing the opening to the trachea. These movements produce a larger area for food to pass through, while preventing food and beverages from entering the trachea.

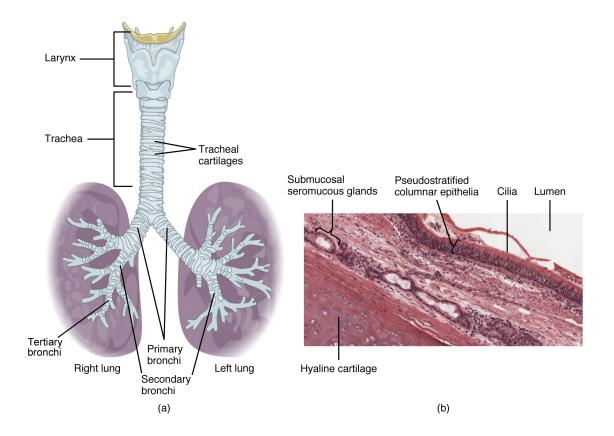
The upper portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the back of throat, where it can be swallowed down the esophagus.

Trachea

The trachea (windpipe) extends from the larynx toward the lungs ([link]a). The trachea is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The connective tissue allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. Similar to the larynx, the trachea is lined with goblet cells and cilia. The goblet cells produce mucus that traps debris while the cilia move the trapped debris into the back of the throat where it can be swallowed and enter the esophagus.

Trachea

(a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM × 1220. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Bronchial Tree

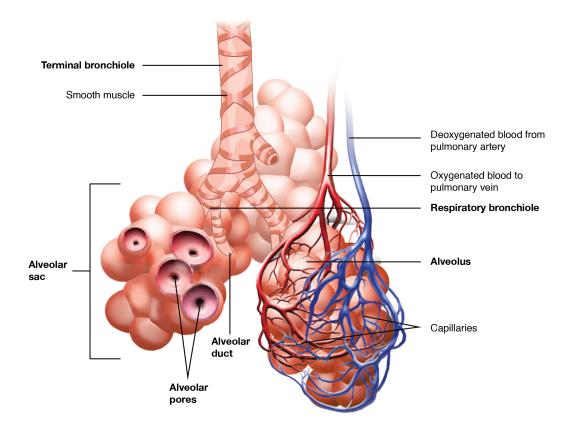
These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells ([link]b). The carina is a raised structure that conRings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The right and left primary bronchi branch into smaller diameter tubes with many branches called secondary bronchi (also called lobar bronchi). The secondary bronchi branch into even smaller diameter branches called tertiary bronchi (also called segmental bronchi) and finally those branch into even smaller branches called bronchioles. A bronchial tree (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide

a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens.

Bronchioles, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles. The terminal bronchioles are the last structure of the conducting zone and will lead to the structures of gas exchange. There are more than 1000 terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. These structures include the respiratory structures include the respiratory bronchioles, alveolar ducts, and alveoli. The respiratory zone begins where the terminal bronchioles join a **respiratory bronchiole**, the smallest type of bronchiole ([link]), which then leads to an alveolar duct, opening into a cluster of alveoli. Respiratory Zone



Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

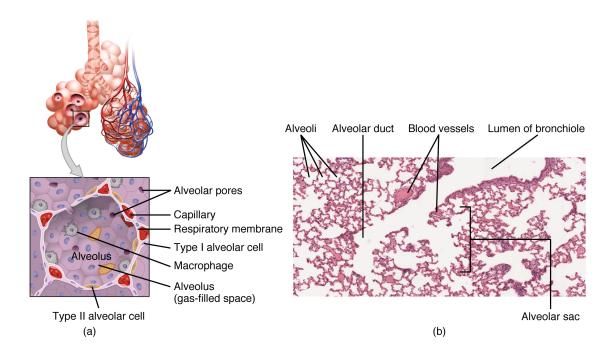
Alveoli

An **alveolar duct** is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An **alveolus** is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An **alveolar sac** is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 µm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by **alveolar pores**, which help maintain equal air pressure throughout the alveoli and lung ([link]).

Structures of the Respiratory Zone

(a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178.(Micrograph provided by the Regents of University of Michigan Medical School © 2012)



The alveolar wall consists of three major cell types: type I alveolar cells, type II alveolar cells, and alveolar macrophages. A **type I alveolar cell** is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. Type I cells form the wall of the alveoli. **type II alveolar cell** is interspersed among the type I cells and secretes **pulmonary surfactant**, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli by breaking hydrogen bonds in water molecules. Pulmonary surfactant allows the lungs to expand easily during respiration. Roaming around the alveolar wall is the **alveolar macrophage**, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and

borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a **respiratory membrane** that is approximately 0.5 mm thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO_2 to be released into the air of the alveoli.

Note:

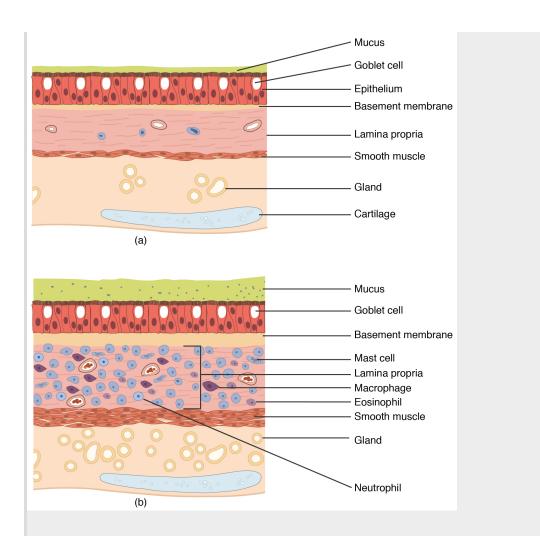
Diseases of the...

Respiratory System: Asthma

Asthma is common condition that affects the lungs in both adults and children. Approximately 8.2 percent of adults (18.7 million) and 9.4 percent of children (7 million) in the United States suffer from asthma. In addition, asthma is the most frequent cause of hospitalization in children. Asthma is a chronic disease characterized by inflammation and edema of the airway, and bronchospasms (that is, constriction of the bronchioles), which can inhibit air from entering the lungs. In addition, excessive mucus secretion can occur, which further contributes to airway occlusion ([link]). Cells of the immune system, such as eosinophils and mononuclear cells, may also be involved in infiltrating the walls of the bronchi and bronchioles.

Bronchospasms occur periodically and lead to an "asthma attack." An attack may be triggered by environmental factors such as dust, pollen, pet hair, or dander, changes in the weather, mold, tobacco smoke, and respiratory infections, or by exercise and stress.

Normal and Bronchial Asthma Tissues



(a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the condition, frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that

are used to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer. In many cases, the underlying cause of the condition is unknown. However, recent research has demonstrated that certain viruses, such as human rhinovirus C (HRVC), and the bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are contracted in infancy or early childhood, may contribute to the development of many cases of asthma.

Note:



Visit this <u>site</u> to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Note:



Watch this <u>video</u> to learn more about the bronchial tree.

Chapter Review

The respiratory system is responsible for obtaining oxygen and getting rid of carbon dioxide, and aiding in speech production and in sensing odors. From a functional perspective, the respiratory system can be divided into two major areas: the conducting zone and the respiratory zone. The conducting zone consists of all of the structures that provide passageways for air to travel into and out of the lungs: the nasal cavity, pharynx, trachea, bronchi, and most bronchioles. The respiratory zone includes the structures of the lung that are directly involved in gas exchange: the terminal bronchioles and alveoli.

The lining of the conducting zone is composed mostly of pseudostratified ciliated columnar epithelium with goblet cells. The mucus traps pathogens and debris, whereas beating cilia move the mucus superiorly toward the throat, where it is swallowed. As the bronchioles become smaller and smaller, and nearer the alveoli, the epithelium thins and is simple squamous epithelium in the alveoli. The endothelium of the surrounding capillaries, together with the alveolar epithelium, forms the respiratory membrane. This is a blood-air barrier through which gas exchange occurs by simple diffusion.

Glossary

alveolar duct

small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli

alveolar macrophage

immune system cell of the alveolus that removes debris and pathogens

alveolar pore

opening that allows airflow between neighboring alveoli

alveolar sac

cluster of alveoli

alveolus

small, grape-like sac that performs gas exchange in the lungs

bronchial tree

collective name for the multiple branches of the bronchi and bronchioles of the respiratory system

bronchiole

branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

bronchus

tube connected to the trachea that branches into many subsidiaries and provides a passageway for air to enter and leave the lungs

conducting zone

region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange

epiglottis

leaf-shaped piece of elastic cartilage that is a portion of the larynx that swings to close the trachea during swallowing

glottis

opening between the vocal folds through which air passes when producing speech

larynx

cartilaginous structure that produces the voice, prevents food and beverages from entering the trachea, and regulates the volume of air that enters and leaves the lungs

pharynx

region of the conducting zone that forms a tube of skeletal muscle lined with respiratory epithelium; located between the nasal conchae and the esophagus and trachea

pulmonary surfactant

substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells

respiratory bronchiole

specific type of bronchiole that leads to alveolar sacs

respiratory epithelium

ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus

respiratory membrane

alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases

respiratory zone

includes structures of the respiratory system that are directly involved in gas exchange

trachea

tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung

type I alveolar cell

squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

type II alveolar cell

cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant

OU Human Physiology: The Lungs By the end of this section, you will be able to:

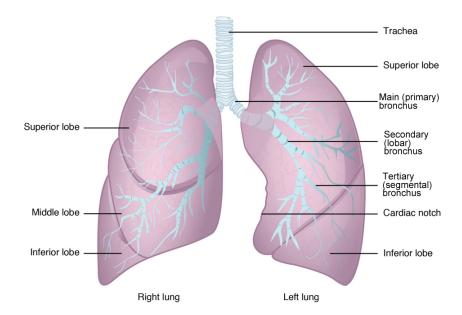
- Describe the overall function of the lung
- Summarize the blood flow pattern associated with the lungs
- Describe the pleura of the lungs and their function
- Explain the importance of the pleural cavity

A major organ of the respiratory system, each **lung** houses structures of both the conducting and respiratory zones. The main function of the lungs is to perform the exchange of oxygen and carbon dioxide with air from the atmosphere. To this end, the lungs exchange respiratory gases across a very large epithelial surface area—about 70 square meters—that is highly permeable to gases.

Gross Anatomy of the Lungs

The lungs are pyramid-shaped, paired organs that are connected to the trachea by the right and left bronchi; on the inferior surface, the lungs are bordered by the diaphragm. The diaphragm is the flat, dome-shaped muscle located at the base of the lungs and thoracic cavity. The lungs are enclosed by the pleurae, which are attached to the mediastinum. The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right. The **cardiac notch** is an indentation on the surface of the left lung, and it allows space for the heart ([link]).

Gross Anatomy of the Lungs



Each lung is composed of smaller units called lobes. Fissures separate these lobes from each other. The right lung consists of three lobes. The left lung consists of two lobes. A bronchopulmonary segment is a division of a lobe, and each lobe houses multiple bronchopulmonary segments. Each segment receives air from its own tertiary bronchus and is supplied with blood by its own artery. Some diseases of the lungs typically affect one or more bronchopulmonary segments, and in some cases, the diseased segments can be surgically removed with little influence on neighboring segments.

Blood Supply and Nervous Innervation of the Lungs

The blood supply of the lungs plays an important role in gas exchange and serves as a transport system for gases throughout the body. In addition, innervation by the both the parasympathetic and sympathetic nervous systems provides an important level of control through dilation and constriction of the airway.

Blood Supply

The major function of the lungs is to perform gas exchange, which requires blood from the pulmonary circulation. This blood supply contains deoxygenated blood and travels to the lungs where erythrocytes, also known as red blood cells, pick up oxygen to be transported to tissues throughout the body. The **pulmonary artery** is an artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli. The pulmonary artery branches multiple times as it follows the bronchi, and each branch becomes progressively smaller in diameter. One arteriole and an accompanying venule supply and drain one pulmonary lobule. As they near the alveoli, the pulmonary arteries become the pulmonary capillary network. The pulmonary capillary network consists of tiny vessels with very thin walls that lack smooth muscle fibers. The capillaries branch and follow the bronchioles and structure of the alveoli. It is at this point that the capillary wall meets the alveolar wall, creating the respiratory membrane. Once the blood is oxygenated, it drains from the alveoli by way of multiple pulmonary veins.

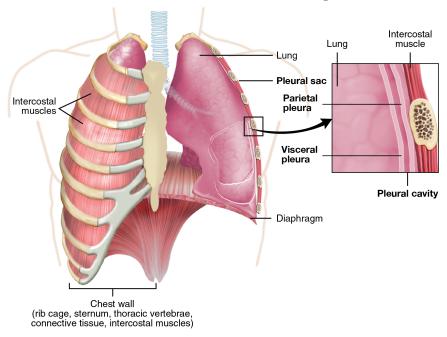
Nervous Innervation

Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems. The parasympathetic system causes **bronchoconstriction**, whereas the sympathetic nervous system stimulates **bronchodilation**. Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control.

Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The **visceral pleura** is the layer that is superficial to the lungs ([link]). In contrast, the **parietal pleura** is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The **pleural cavity** is the space between the visceral and parietal layers.

Parietal and Visceral Pleurae of the Lungs



The pleurae perform two major functions: They produce pleural fluid and create cavities that separate the major organs. **Pleural fluid** is secreted from both pleural layers and acts to lubricate their surfaces. This lubrication reduces friction between the two layers to prevent trauma during breathing, and creates surface tension that helps maintain the position of the lungs against the thoracic wall. This adhesive characteristic of the pleural fluid causes the lungs to enlarge when the thoracic wall expands during ventilation, allowing the lungs to fill with air. The pleurae also create a division between major organs that prevents interference due to the movement of the organs, while preventing the spread of infection.

Note:

Everyday Connection

The Effects of Second-Hand Tobacco Smoke

The burning of a tobacco cigarette creates multiple chemical compounds that are released through mainstream smoke, which is inhaled by the smoker, and through sidestream smoke, which is the smoke that is given off by the burning cigarette. Second-hand smoke, which is a combination of sidestream smoke and the mainstream smoke that is exhaled by the

smoker, has been demonstrated by numerous scientific studies to cause disease. At least 40 chemicals in sidestream smoke have been identified that negatively impact human health, leading to the development of cancer or other conditions, such as immune system dysfunction, liver toxicity, cardiac arrhythmias, pulmonary edema, and neurological dysfunction. Furthermore, second-hand smoke has been found to harbor at least 250 compounds that are known to be toxic, carcinogenic, or both. Some major classes of carcinogens in second-hand smoke are polyaromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, formaldehyde, and acetaldehyde.

Tobacco and second-hand smoke are considered to be carcinogenic. Exposure to second-hand smoke can cause lung cancer in individuals who are not tobacco users themselves. It is estimated that the risk of developing lung cancer is increased by up to 30 percent in nonsmokers who live with an individual who smokes in the house, as compared to nonsmokers who are not regularly exposed to second-hand smoke. Children are especially affected by second-hand smoke. Children who live with an individual who smokes inside the home have a larger number of lower respiratory infections, which are associated with hospitalizations, and higher risk of sudden infant death syndrome (SIDS). Second-hand smoke in the home has also been linked to a greater number of ear infections in children, as well as worsening symptoms of asthma.

Note:



Watch this video to learn more about the lungs.

Chapter Review

The lungs are the major organs of the respiratory system and are responsible for performing gas exchange. The lungs are paired and separated into lobes; the left lung consists of two lobes, whereas the right lung consists of three lobes. Blood circulation is very important, as blood is required to transport oxygen from the lungs to other tissues throughout the body. The function of the pulmonary circulation is to aid in gas exchange. The pulmonary artery provides deoxygenated blood to the capillaries that form respiratory membranes with the alveoli, and the pulmonary veins return newly oxygenated blood to the heart for further transport throughout the body. The lungs are innervated by the parasympathetic and sympathetic nervous systems, which coordinate the bronchodilation and bronchoconstriction of the airways. The lungs are enclosed by the pleura, a membrane that is composed of visceral and parietal pleural layers. The space between these two layers is called the pleural cavity. The cells of the pleural membrane create pleural fluid, which serves as both a lubricant (to reduce friction during breathing) and as an adhesive to adhere the lungs to the thoracic wall (to facilitate movement of the lungs during ventilation).

Glossary

bronchoconstriction

decrease in the size of the bronchiole due to contraction of the muscular wall

bronchodilation

increase in the size of the bronchiole due to contraction of the muscular wall

cardiac notch

indentation on the surface of the left lung that allows space for the heart

lung

organ of the respiratory system that performs gas exchange

parietal pleura

outermost layer of the pleura that connects to the thoracic wall, mediastinum, and diaphragm

pleural cavity

space between the visceral and parietal pleurae

pleural fluid

substance that acts as a lubricant for the visceral and parietal layers of the pleura during the movement of breathing

pulmonary artery

artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli

visceral pleura

innermost layer of the pleura that is superficial to the lungs and extends into the lung fissures

OU Human Physiology: The Process of Breathing By the end of this section, you will be able to:

- Discuss how pressure and volume are related according to Boyle's law
- Compare and contrast the atmospheric, intra-alveoloar, and intrapleural pressures
- Demonstrate the natural tendencies of the thoracic wall and lung wall and why the atmospheric, intra-alveoloar, and intrapleural pressures must exist to prevent these natural tendencies
- Infer how changes in pressure gradients and resistance will alter air flow and therefore pulmonary ventilation
- Describe the process of eupnea
- Describe the process of hyperpnea
- Compare and contrast the respiratory volumes and capacities
- Explain the importance of pulmonary function tests using a spirometer
- Define respiratory rate and its importance
- Identify the location of the respiratory centers
- List the variables that will stimulate the respiratory center
- Describe how changes in carbon dioxide plasma levels can alter hydrogen ion concentration and therefore plasma pH
- Describe the mechanism of the peripheral and central chemoreceptors in maintaining the respiratory rate and depth of breathing

Pulmonary ventilation is the act of breathing, which can be described as the movement of air into and out of the lungs. The major mechanisms that drive pulmonary ventilation are atmospheric pressure (P_{atm}); the air pressure within the alveoli, called alveolar pressure (P_{alv}); and the pressure within the pleural cavity, called intrapleural pressure (P_{ip}).

Mechanisms of Breathing

The alveolar and intrapleural pressures are dependent on certain physical features of the lung. However, the ability to breathe—to have air enter the lungs during inspiration and air leave the lungs during expiration—is dependent on the air pressure of the atmosphere and the air pressure within the lungs.

Pressure Relationships

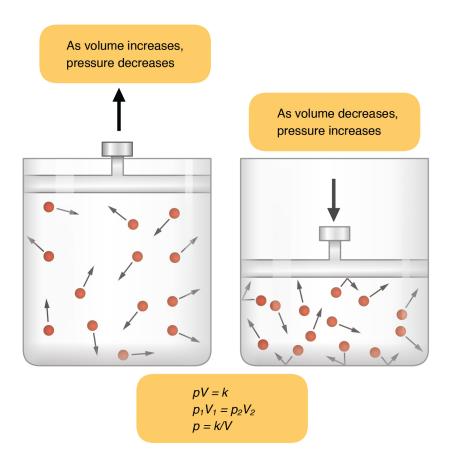
Inspiration (or inhalation) and expiration (or exhalation) are dependent on the differences in pressure between the atmosphere and the lungs. In a gas, pressure is a force created by the movement of gas molecules that are confined. For example, a certain number of gas molecules in a two-liter container has more room than the same number of gas molecules in a oneliter container ([link]). In this case, the force exerted by the movement of the gas molecules against the walls of the two-liter container is lower than the force exerted by the gas molecules in the one-liter container. Therefore, the pressure is lower in the two-liter container and higher in the one-liter container. At a constant temperature, changing the volume occupied by the gas changes the pressure, as does changing the number of gas molecules. **Boyle's law** describes the relationship between volume and pressure in a gas at a constant temperature. Boyle discovered that the pressure of a gas is inversely proportional to its volume: If volume increases, pressure decreases. Likewise, if volume decreases, pressure increases. Pressure and volume are inversely related (P = k/V). Therefore, the pressure in the oneliter container (one-half the volume of the two-liter container) would be twice the pressure in the two-liter container. Boyle's law is expressed by the following formula:

Equation:

$$P_1V_1 = P_2V_2$$

In this formula, P_1 represents the initial pressure and V_1 represents the initial volume, whereas the final pressure and volume are represented by P_2 and V_2 , respectively. If the two- and one-liter containers were connected by a tube and the volume of one of the containers were changed, then the gases would move from higher pressure (lower volume) to lower pressure (higher volume).

Boyle's Law



In a gas, pressure increases as volume decreases.

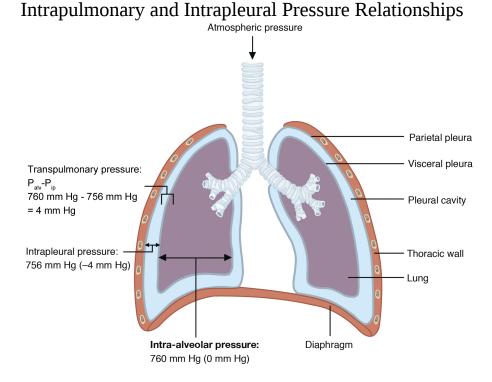




Watch this <u>video</u> to learn more about Boyle's Law.

Pulmonary ventilation is dependent on three types of pressure: atmospheric, intra-alveolar, and interpleural. **Atmospheric pressure** is the amount of force that is exerted by gases in the air surrounding any given surface, such as the body. Atmospheric pressure can be expressed in terms of the unit atmosphere, abbreviated atm, or in millimeters of mercury (mm Hg). One atm is equal to 760 mm Hg, which is the atmospheric pressure at sea level. Typically, for respiration, other pressure values are discussed in relation to atmospheric pressure. Therefore, negative pressure is pressure lower than the atmospheric pressure, whereas positive pressure is pressure that it is greater than the atmospheric pressure. A pressure that is equal to the atmospheric pressure is expressed as zero.

Intra-alveolar pressure is the pressure of the air within the alveoli, which changes during the different phases of breathing ([link]). Because the alveoli are connected to the atmosphere via the tubing of the airways (similar to the two- and one-liter containers in the example above), the pressure of the alveoli always equalizes with the atmospheric pressure.



Alveolar pressure changes during the different phases of the cycle. It equalizes at 760 mm Hg but does not remain at 760 mm Hg.

Intrapleural pressure is the pressure of the air within the pleural cavity, between the visceral and parietal pleurae. Similar to intra-alveolar pressure, intrapleural pressure also changes during the different phases of breathing. However, due to certain characteristics of the lungs, the intrapleural pressure is always lower than, or negative to, the intra-alveolar pressure (and therefore also to atmospheric pressure). Although it fluctuates during inspiration and expiration, intrapleural pressure remains approximately –4 mm Hg throughout the breathing cycle.

Competing forces within the thorax cause the formation of the negative intrapleural pressure. One of these forces relates to the elasticity of the lungs themselves—elastic tissue pulls the lungs inward, away from the thoracic wall. Surface tension of alveolar fluid, which is mostly water, also creates an inward pull of the lung tissue. This inward tension from the lungs is countered by opposing forces from the pleural fluid and thoracic wall. Surface tension within the pleural cavity pulls the lungs outward. Too much or too little pleural fluid would hinder the creation of the negative intrapleural pressure; therefore, the level must be closely monitored and drained by the lymphatic system. Since the parietal pleura is attached to the thoracic wall, the natural elasticity of the chest wall opposes the inward pull of the lungs. Ultimately, the outward pull is slightly greater than the inward pull, creating the –4 mm Hg intrapleural pressure relative to the intraalveolar pressure. **Transpulmonary pressure** is the difference between the intrapleural and intra-alveolar pressures, and it determines the size of the lungs. A higher transpulmonary pressure corresponds to a larger lung.

Physical Factors Affecting Ventilation

In addition to the differences in pressures, breathing is also dependent upon the contraction and relaxation of muscle fibers of both the diaphragm and thorax. The lungs themselves are passive during breathing, meaning they are not involved in creating the movement that helps inspiration and expiration. This is because of the adhesive nature of the pleural fluid, which allows the lungs to be pulled outward when the thoracic wall moves during inspiration. The recoil of the thoracic wall during expiration causes compression of the lungs. Contraction and relaxation of the diaphragm and intercostals muscles (found between the ribs) cause most of the pressure changes that result in inspiration and expiration. These muscle movements and subsequent pressure changes cause air to either rush in or be forced out of the lungs.

Other characteristics of the lungs influence the effort that must be expended to ventilate. Resistance is a force that slows motion, in this case, the flow of gases. The size of the airway is the primary factor affecting resistance. A small tubular diameter forces air through a smaller space, causing more collisions of air molecules with the walls of the airways. The following formula helps to describe the relationship between airway resistance and pressure changes:

Equation:

$$F = \Delta P/R$$

F is the force of air flow and relies on a pressure gradient. Air flows from a high pressure gradient toward a low pressure gradient. The pressure gradient is determined by ΔP which is the difference between atmospheric pressure (P_{atm}) and intra-alveolar pressure (P_{alv}) (P_{atm} - P_{alv}). As air flows through a tube it encounters resistance (R). Resistance is related to the radius of the airway and the amount of mucus in airway. Since atmospheric pressure remains constant during breathing, the changes in intra-alveolar pressure will change the pressure gradient and therefore air flow (F).

As noted earlier, there is surface tension within the alveoli caused by water present in the lining of the alveoli. This surface tension tends to inhibit expansion of the alveoli. However, pulmonary surfactant secreted by type II alveolar cells mixes with that water and helps reduce this surface tension. Without pulmonary surfactant, the alveoli would collapse during expiration.

Thoracic wall compliance is the ability of the thoracic wall to stretch while under pressure. This can also affect the effort expended in the process of breathing. In order for inspiration to occur, the thoracic cavity must

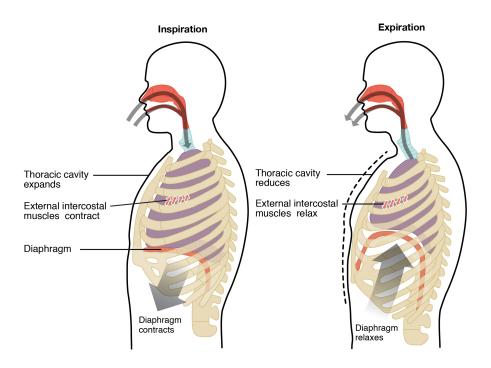
expand. The expansion of the thoracic cavity directly influences the capacity of the lungs to expand. If the tissues of the thoracic wall are not very compliant, it will be difficult to expand the thorax to increase the size of the lungs.

Pulmonary Ventilation

The difference in pressures drives pulmonary ventilation because air flows down a pressure gradient, that is, air flows from an area of higher pressure to an area of lower pressure. Air flows into the lungs largely due to a difference in pressure; atmospheric pressure is greater than intra-alveolar pressure, and intra-alveolar pressure is greater than intrapleural pressure. Air flows out of the lungs during expiration based on the same principle; pressure within the lungs becomes greater than the atmospheric pressure.

Pulmonary ventilation comprises two major steps: inspiration and expiration. **Inspiration** is an active process that causes air to enter the lungs, and **expiration** is the process that causes air to leave the lungs ([link]). Expiration can be passive or active. A **respiratory cycle** is one sequence of inspiration and expiration. In general, two muscle groups are used during normal inspiration: the diaphragm and the external intercostal muscles. Additional muscles can be used if a bigger breath is required. When the diaphragm contracts, it moves inferiorly toward the abdominal cavity, creating a larger thoracic cavity and more space for the lungs. Contraction of the external intercostal muscles moves the ribs upward and outward, causing the rib cage to expand, which increases the volume of the thoracic cavity. Due to the adhesive force of the pleural fluid, the expansion of the thoracic cavity forces the lungs to stretch and expand as well. This increase in volume leads to a decrease in intra-alveolar pressure, creating a pressure lower than atmospheric pressure. As a result, a pressure gradient is created that drives air into the lungs.

Inspiration and Expiration



Inspiration and expiration occur due to the expansion and contraction of the thoracic cavity, respectively.

The process of normal expiration is passive, meaning that energy is not required to push air out of the lungs. Instead, the elasticity of the lung tissue causes the lung to recoil, as the diaphragm and intercostal muscles relax following inspiration. In turn, the thoracic cavity and lungs decrease in volume, causing an increase in intra-alveolar pressure. The intra-alveolar pressure rises above atmospheric pressure, creating a pressure gradient that causes air to leave the lungs.

There are different types, or modes, of breathing that require a slightly different process to allow inspiration and expiration. **Quiet breathing**, also known as eupnea, is a mode of breathing that occurs at rest and does not require the cognitive thought of the individual. During quiet breathing, the diaphragm and external intercostals must contract.

In contrast, **forced breathing**, also known as hyperpnea, is a mode of breathing that can occur during exercise or actions that require the active

manipulation of breathing, such as singing. During forced breathing, inspiration and expiration both occur due to muscle contractions. In addition to the contraction of the diaphragm and intercostal muscles, other accessory muscles must also contract. During forced inspiration, muscles of the neck, including the scalenes, contract and lift the thoracic wall, increasing lung volume. During forced expiration, muscles of the abdomen contract, forcing abdominal organs upward against the diaphragm. This helps to push the diaphragm further into the thorax, pushing more air out. In addition, the internal intercostals contract to compress the rib cage, which also reduces the volume of the thoracic cavity.

Note:



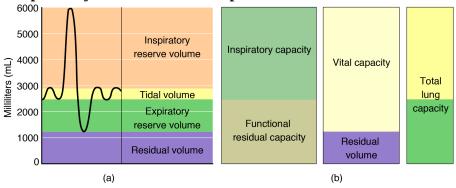
Watch this video to learn more about inhalation and exhalation.

Respiratory Volumes and Capacities

Respiratory volume is the term used for various volumes of air moved by or associated with the lungs at a given point in the respiratory cycle. There are four major types of respiratory volumes: tidal, residual, inspiratory reserve, and expiratory reserve ([link]). **Tidal volume (TV)** is the amount of air that normally enters and exits the lungs during quiet breathing, which is about 500 milliliters. **Expiratory reserve volume (ERV)** is the amount of air you can forcefully exhale past a normal tidal expiration, up to 1200 milliliters for men. **Inspiratory reserve volume (IRV)** is produced by a deep inhalation, past a tidal inspiration. This is the extra volume that can be brought into the lungs during a forced inspiration. **Residual volume (RV)** is the air left in the lungs if you exhale as much air as possible. The residual

volume makes breathing easier by preventing the alveoli from collapsing. Respiratory volume is dependent on a variety of factors, and measuring the different types of respiratory volumes can provide important clues about a person's respiratory health ([link]). Respiratory volumes are measured by using a spirometer.

Respiratory Volumes and Capacities



These two graphs show (a) respiratory volumes and (b) the combination of volumes that results in respiratory capacity.

Pulmonary Function Testing

Pulmonary function test	Instrument	Measures	Function
	Spirometer	Forced vital capacity (FVC)	Volume of air that is exhaled after maximum inhalation
		Forced expiratory volume (FEV)	Volume of air exhaled in one breath
		Forced expiratory flow, 25–75 percent	Air flow in the middle of exhalation
		Peak expiratory flow (PEF)	Rate of exhalation
Spirometry		Maximum voluntary ventilation (MVV)	Volume of air that can be inspired and expired in 1 minute
		Slow vital capacity (SVC)	Volume of air that can be slowly exhaled after inhaling past the tidal volume
		Total lung capacity (TLC)	Volume of air in the lungs after maximum inhalation
		Functional residual capacity (FRC)	Volume of air left in the lungs after normal expiration
		Residual volume (RV)	Volume of air in the lungs after maximum exhalation
		Total lung capacity (TLC)	Maximum volume of air that the lungs can hold
		Expiratory reserve volume (ERV)	The volume of air that can be exhaled beyond normal exhalation
Gas diffusion	Blood gas analyzer	Arterial blood gases	Concentration of oxygen and carbon dioxide in the blood

Respiratory capacity is the combination of two or more selected volumes, which further describes the amount of air in the lungs during a given time. For example, **total lung capacity (TLC)** is the sum of all of the lung volumes (TV, ERV, IRV, and RV), which represents the total amount of air a person can hold in the lungs after a forceful inhalation. TLC is about 6000 mL air for men, and about 4200 mL for women. **Vital capacity (VC)** is the amount of air a person can move into or out of his or her lungs, and is the sum of all of the volumes except residual volume (TV, ERV, and IRV), which is between 4000 and 5000 milliliters. **Inspiratory capacity (IC)** is the maximum amount of air that can be inhaled past a normal tidal expiration, is the sum of the tidal volume and inspiratory reserve volume. On the other hand, the **functional residual capacity (FRC)** is the amount of air that remains in the lung after a normal tidal expiration; it is the sum of expiratory reserve volume and residual volume (see [link]).

Note:



Watch this <u>video</u> to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

In addition to the air that creates respiratory volumes, the respiratory system also contains **anatomical dead space**, which is air that is present in the airway that never reaches the alveoli and therefore never participates in gas exchange. **Alveolar dead space** involves air found within alveoli that are unable to function, such as those affected by disease or abnormal blood flow. **Total dead space** is the anatomical dead space and alveolar dead

space together, and represents all of the air in the respiratory system that is not being used in the gas exchange process.

Respiratory Rate and Control of Ventilation

Breathing usually occurs without thought, although at times you can consciously control it, such as when you swim under water, sing a song, or blow bubbles. The **respiratory rate** is the total number of breaths, or respiratory cycles, that occur each minute. Respiratory rate can be an important indicator of disease, as the rate may increase or decrease during an illness or in a disease condition. The respiratory rate is controlled by the respiratory center located within the medulla oblongata in the brain, which responds primarily to changes in carbon dioxide, oxygen, and pH levels in the blood. The pons also contains a respiratory center that communicates with those neurons in the medulla oblongata. The pons respiratory center will respond to changes in CO2 and pH. Both of these respiratory centers are composed of clusters of neurons that will determine how fast and how often we should be breathing.

The normal respiratory rate of a child decreases from birth to adolescence. A child under 1 year of age has a normal respiratory rate between 30 and 60 breaths per minute, but by the time a child is about 10 years old, the normal rate is closer to 18 to 30. By adolescence, the normal respiratory rate is similar to that of adults, 12 to 18 breaths per minute.

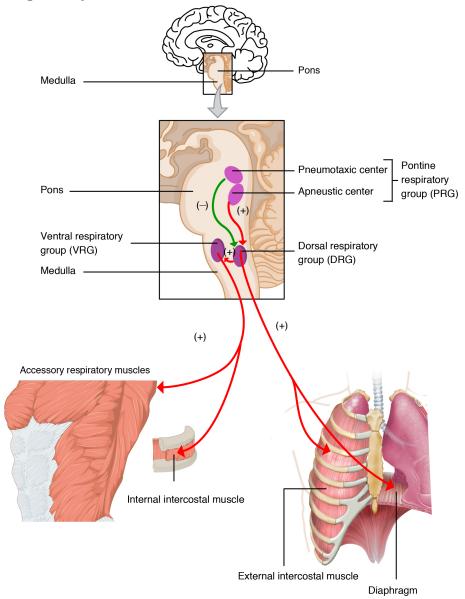
Ventilation Control Centers

The control of ventilation is a complex interplay of multiple regions in the brain that signal the muscles used in pulmonary ventilation to contract ([link]). The result is typically a rhythmic, consistent ventilation rate that provides the body with sufficient amounts of oxygen, while adequately removing carbon dioxide.

Summary of Ventilation Regulation			
System component	Function		
Medullary respiratory renter	Sets the basic rhythm of breathing		
Ventral respiratory group (VRG)	Generates the breathing rhythm and integrates data coming into the medulla		
Dorsal respiratory group (DRG)	Integrates input from the stretch receptors and the chemoreceptors in the periphery		
Pons respiratory center (Pontine Respiratory Group; PRG)	Influences and modifies the medulla oblongata's functions		
Aortic body	Monitors blood PCO ₂ , PO ₂ , and pH		
Carotid body	Monitors blood PCO ₂ , PO ₂ , and pH		
Hypothalamus	Monitors emotional state and body temperature		
Cortical areas of the brain	Control voluntary breathing		
Proprioceptors	Send impulses regarding joint and muscle movements		
Pulmonary irritant reflexes	Protect the respiratory zones of the system from foreign material		
Inflation reflex	Protects the lungs from over-inflating		

Neurons that innervate the muscles of the respiratory system are responsible for controlling and regulating pulmonary ventilation. The major brain centers involved in pulmonary ventilation are the medulla oblongata and the pontine respiratory group located in the pons([link]).

Respiratory Centers of the Brain



The medulla oblongata contains the **dorsal respiratory group (DRG)** and the **ventral respiratory group (VRG)**. The DRG is involved in maintaining a constant breathing rhythm by stimulating the diaphragm and intercostal muscles to contract, resulting in inspiration. When activity in the DRG ceases, it no longer stimulates the diaphragm and intercostals to

contract, allowing them to relax, resulting in expiration. The VRG is involved in forced breathing, as the neurons in the VRG stimulate the accessory muscles involved in forced breathing to contract, resulting in forced inspiration. The VRG also stimulates the accessory muscles involved in forced expiration to contract.

The second respiratory center of the brain is located within the pons, called the pontine respiratory group, and consists of the apneustic and pneumotaxic centers. The **apneustic center** is a double cluster of neuronal cell bodies that stimulate neurons in the DRG, controlling the depth of inspiration, particularly for deep breathing. The **pneumotaxic center** is a network of neurons that inhibits the activity of neurons in the DRG, allowing relaxation after inspiration, and thus controlling the overall rate.

Factors That Affect the Rate and Depth of Respiration

The respiratory rate and the depth of inspiration are regulated by the medulla oblongata and pons; however, these regions of the brain do so in response to systemic stimuli. It is a dose-response, positive-feedback relationship in which the greater the stimulus, the greater the response. Thus, increasing stimuli results in forced breathing. Multiple systemic factors are involved in stimulating the brain to produce pulmonary ventilation.

The major factor that stimulates the medulla oblongata and pons to produce respiration is surprisingly not oxygen concentration, but rather the concentration of carbon dioxide in the blood. As you recall, carbon dioxide is a waste product of cellular respiration and can be toxic. Concentrations of chemicals are sensed by chemoreceptors. **Central chemoreceptors** are one of the specialized receptors that are located in the medulla and pons, whereas **peripheral chemoreceptors** (also called glomus cells) are one of the specialized receptors located in the carotid arteries. Please note that there are peripheral chemoreceptors in the aortic arch in other animals. Humans lack these receptors in the aortic arch. Hence we will only focus on the carotid peripheral chemoreceptors. Concentration changes in certain substances, such as carbon dioxide or hydrogen ions, stimulate these

receptors, which in turn signal the respiratory centers of the brain. In the case of carbon dioxide, as the concentration of CO2 in the blood increases, it readily diffuses across the blood-brain barrier, where it collects in the extracellular fluid. As will be explained in more detail later, increased carbon dioxide levels lead to increased levels of hydrogen ions, decreasing pH. The increase in hydrogen ions in the brain triggers the central chemoreceptors to stimulate the respiratory centers to initiate contraction of the diaphragm and intercostal muscles. As a result, the rate and depth of respiration increase, allowing more carbon dioxide to be expelled, which brings more air into and out of the lungs promoting a reduction in the blood levels of carbon dioxide, and therefore hydrogen ions, in the blood. In contrast, low levels of carbon dioxide in the blood cause low levels of hydrogen ions in the brain, leading to a decrease in the rate and depth of pulmonary ventilation, producing shallow, slow breathing.

Another factor involved in influencing the respiratory activity of the brain is systemic arterial concentrations of hydrogen ions. Increasing carbon dioxide levels can lead to increased H⁺ levels, as mentioned above, as well as other metabolic activities, such as lactic acid accumulation after strenuous exercise. Peripheral chemoreceptors of the aortic arch and carotid arteries sense arterial levels of hydrogen ions. When peripheral chemoreceptors sense decreasing, or more acidic, pH levels, they stimulate an increase in ventilation to remove carbon dioxide from the blood at a quicker rate. Removal of carbon dioxide from the blood helps to reduce hydrogen ions, thus increasing systemic pH.

Blood levels of oxygen are also important in influencing respiratory rate. The peripheral chemoreceptors are responsible for sensing large changes in blood oxygen levels. If blood oxygen levels become quite low—about 60 mm Hg or less— peripheral chemoreceptors stimulate an increase in respiratory activity. The chemoreceptors are only able to sense dissolved oxygen molecules, not the oxygen that is bound to hemoglobin. As you recall, the majority of oxygen is bound by hemoglobin; when dissolved levels of oxygen drop, hemoglobin releases oxygen. Therefore, a large drop in oxygen levels is required to stimulate the chemoreceptors of the carotid arteries.

The hypothalamus and other brain regions associated with the limbic system also play roles in influencing the regulation of breathing by interacting with the respiratory centers. The hypothalamus and other regions associated with the limbic system are involved in regulating respiration in response to emotions, pain, and temperature. For example, an increase in body temperature causes an increase in respiratory rate. Feeling excited or the fight-or-flight response will also result in an increase in respiratory rate.

Note:

Disorders of the...

Respiratory System: Sleep Apnea

Sleep apnea is a chronic disorder that can occur in children or adults, and is characterized by the cessation of breathing during sleep. These episodes may last for several seconds or several minutes, and may differ in the frequency with which they are experienced. Sleep apnea leads to poor sleep, which is reflected in the symptoms of fatigue, evening napping, irritability, memory problems, and morning headaches. In addition, many individuals with sleep apnea experience a dry throat in the morning after waking from sleep, which may be due to excessive snoring. There are two types of sleep apnea: obstructive sleep apnea and central sleep apnea. Obstructive sleep apnea is caused by an obstruction of the airway during sleep, which can occur at different points in the airway, depending on the underlying cause of the obstruction. For example, the tongue and throat muscles of some individuals with obstructive sleep apnea may relax excessively, causing the muscles to push into the airway. Another example is obesity, which is a known risk factor for sleep apnea, as excess adipose tissue in the neck region can push the soft tissues towards the lumen of the airway, causing the trachea to narrow. In central sleep apnea, the respiratory centers of the brain do not respond properly to rising carbon dioxide levels and therefore do not stimulate the contraction of the diaphragm and intercostal muscles regularly. As a result, inspiration does not occur and breathing stops for a short period. In some cases, the cause of central sleep apnea is unknown. However, some medical conditions, such as stroke and congestive heart failure, may cause

damage to the pons or medulla oblongata. In addition, some pharmacologic agents, such as morphine, can affect the respiratory centers, causing a decrease in the respiratory rate. The symptoms of central sleep apnea are similar to those of obstructive sleep apnea.

A diagnosis of sleep apnea is usually done during a sleep study, where the patient is monitored in a sleep laboratory for several nights. The patient's blood oxygen levels, heart rate, respiratory rate, and blood pressure are monitored, as are brain activity and the volume of air that is inhaled and exhaled. Treatment of sleep apnea commonly includes the use of a device called a continuous positive airway pressure (CPAP) machine during sleep. The CPAP machine has a mask that covers the nose, or the nose and mouth, and forces air into the airway at regular intervals. This pressurized air can help to gently force the airway to remain open, allowing more normal ventilation to occur. Other treatments include lifestyle changes to decrease weight, eliminate alcohol and other sleep apnea—promoting drugs, and changes in sleep position. In addition to these treatments, patients with central sleep apnea may need supplemental oxygen during sleep.

Note:



Watch this <u>video</u> to learn more about how lung volume changes.

Note:					



Watch this <u>video</u> to learn more about peripheral chemoreceptors.

Note:



Watch this <u>video</u> to learn more about central chemoreceptors.

Chapter Review

Pulmonary ventilation is the process of breathing, which is driven by pressure differences between the lungs and the atmosphere. Atmospheric pressure is the force exerted by gases present in the atmosphere. The force exerted by gases within the alveoli is called intra-alveolar (intrapulmonary) pressure, whereas the force exerted by gases in the pleural cavity is called intrapleural pressure. Typically, intrapleural pressure is lower, or negative to, intra-alveolar pressure. The difference in pressure between intrapleural and intra-alveolar pressures is called transpulmonary pressure. In addition, intra-alveolar pressure will equalize with the atmospheric pressure. Pressure is determined by the volume of the space occupied by a gas and is influenced by resistance. Air flows when a pressure gradient is created, from a space of higher pressure to a space of lower pressure. Boyle's law describes the relationship between volume and pressure. A gas is at lower

pressure in a larger volume because the gas molecules have more space to in which to move. The same quantity of gas in a smaller volume results in gas molecules crowding together, producing increased pressure.

Resistance is created by inelastic surfaces, as well as the diameter of the airways. Resistance reduces the flow of gases. The surface tension of the alveoli also influences pressure, as it opposes the expansion of the alveoli. However, pulmonary surfactant helps to reduce the surface tension so that the alveoli do not collapse during expiration. The ability of the lungs to stretch, called lung compliance, also plays a role in gas flow. The more the lungs can stretch, the greater the potential volume of the lungs. The greater the volume of the lungs, the lower the air pressure within the lungs.

Pulmonary ventilation consists of the process of inspiration (or inhalation), where air enters the lungs, and expiration (or exhalation), where air leaves the lungs. During inspiration, the diaphragm and external intercostal muscles contract, causing the rib cage to expand and move outward, and expanding the thoracic cavity and lung volume. This creates a lower pressure within the lung than that of the atmosphere, causing air to be drawn into the lungs. During expiration, the diaphragm and intercostals relax, causing the thorax and lungs to recoil. The air pressure within the lungs increases to above the pressure of the atmosphere, causing air to be forced out of the lungs. However, during forced exhalation, the internal intercostals and abdominal muscles may be involved in forcing air out of the lungs.

Respiratory volume describes the amount of air in a given space within the lungs, or which can be moved by the lung, and is dependent on a variety of factors. Tidal volume refers to the amount of air that enters the lungs during quiet breathing, whereas inspiratory reserve volume is the amount of air that enters the lungs when a person inhales past the tidal volume. Expiratory reserve volume is the extra amount of air that can leave with forceful expiration, following tidal expiration. Residual volume is the amount of air that is left in the lungs after expelling the expiratory reserve volume. Respiratory capacity is the combination of two or more volumes. Anatomical dead space refers to the air within the respiratory structures that never participates in gas exchange, because it does not reach functional

alveoli. Respiratory rate is the number of breaths taken per minute, which may change during certain diseases or conditions.

Both respiratory rate and depth are controlled by the respiratory centers of the brain, which are stimulated by factors such as chemical and pH changes in the blood. These changes are sensed by central chemoreceptors, which are located in the brain, and peripheral chemoreceptors, which are located in the aortic arch and carotid arteries. A rise in carbon dioxide or a decline in oxygen levels in the blood stimulates an increase in respiratory rate and depth.

Glossary

alveolar dead space

air space within alveoli that are unable to participate in gas exchange

anatomical dead space

air space present in the airway that never reaches the alveoli and therefore never participates in gas exchange

apneustic center

network of neurons within the pons that stimulate the neurons in the dorsal respiratory group; controls the depth of inspiration

atmospheric pressure

amount of force that is exerted by gases in the air surrounding any given surface

Boyle's law

relationship between volume and pressure as described by the formula: $P_1V_1 = P_2V_2$

central chemoreceptor

one of the specialized receptors that are located in the brain that sense changes in hydrogen ion, oxygen, or carbon dioxide concentrations in the brain

dorsal respiratory group (DRG)

region of the medulla oblongata that stimulates the contraction of the diaphragm and intercostal muscles to induce inspiration

expiration

(also, exhalation) process that causes the air to leave the lungs

expiratory reserve volume (ERV)

amount of air that can be forcefully exhaled after a normal tidal exhalation

forced breathing

(also, hyperpnea) mode of breathing that occurs during exercise or by active thought that requires muscle contraction for both inspiration and expiration

functional residual capacity (FRC)

sum of ERV and RV, which is the amount of air that remains in the lungs after a tidal expiration

inspiration

(also, inhalation) process that causes air to enter the lungs

inspiratory capacity (IC)

sum of the TV and IRV, which is the amount of air that can maximally be inhaled past a tidal expiration

inspiratory reserve volume (IRV)

amount of air that enters the lungs due to deep inhalation past the tidal volume

intra-alveolar pressure

(intrapulmonary pressure) pressure of the air within the alveoli

intrapleural pressure

pressure of the air within the pleural cavity

peripheral chemoreceptor

one of the specialized receptors located in the aortic arch and carotid arteries that sense changes in pH, carbon dioxide, or oxygen blood levels

pneumotaxic center

network of neurons within the pons that inhibit the activity of the neurons in the dorsal respiratory group; controls rate of breathing

pulmonary ventilation

exchange of gases between the lungs and the atmosphere; breathing

quiet breathing

(also, eupnea) mode of breathing that occurs at rest and does not require the cognitive thought of the individual

residual volume (RV)

amount of air that remains in the lungs after maximum exhalation

respiratory cycle

one sequence of inspiration and expiration

respiratory rate

total number of breaths taken each minute

respiratory volume

varying amounts of air within the lung at a given time

thoracic wall compliance

ability of the thoracic wall to stretch while under pressure

tidal volume (TV)

amount of air that normally enters and exits the lungs during quiet breathing

total dead space

sum of the anatomical dead space and alveolar dead space

total lung capacity (TLC)

total amount of air that can be held in the lungs; sum of TV, ERV, IRV, and RV

transpulmonary pressure

pressure difference between the intrapleural and intra-alveolar pressures

ventral respiratory group (VRG)

region of the medulla oblongata that stimulates the contraction of the accessory muscles involved in respiration to induce forced inspiration and expiration

vital capacity (VC)

sum of TV, ERV, and IRV, which is all the volumes that participate in gas exchange

OU Human Physiology: Gas Exchange By the end of this section, you will be able to:

- Explain how partial pressures are important to gas exchange
- Explain how Henry's law relates to pulmonary ventilation
- Discuss the importance of sufficient ventilation and perfusion, and how the body adapts when they are insufficient
- Discuss the process of external respiration
- Discuss the process of internal respiration

The purpose of the respiratory system is to perform gas exchange. Pulmonary ventilation provides air to the alveoli for this gas exchange process. At the respiratory membrane, where the alveolar and capillary walls meet, gases move across the membranes, with oxygen entering the bloodstream and carbon dioxide exiting. It is through this mechanism that blood is oxygenated and carbon dioxide, the waste product of cellular respiration, is removed from the body.

Gas Exchange

In order to understand the mechanisms of gas exchange in the lung, it is important to understand the underlying principles of gases and their behavior. In addition to Boyle's law, several other gas laws help to describe the behavior of gases.

Gas Laws and Air Composition

Gas molecules exert force on the surfaces with which they are in contact; this force is called pressure. In natural systems, gases are normally present as a mixture of different types of molecules. For example, the atmosphere consists of oxygen, nitrogen, carbon dioxide, and other gaseous molecules, and this gaseous mixture exerts a certain pressure referred to as atmospheric pressure ($[\underline{link}]$). **Partial pressure** (P_x) is the pressure of a single type of gas in a mixture of gases. For example, in the atmosphere, oxygen exerts a partial pressure, and nitrogen exerts another partial pressure, independent of the partial pressure of oxygen ($[\underline{link}]$). **Total pressure** is the sum of all the

partial pressures of a gaseous mixture. **Dalton's law** describes the behavior of nonreactive gases in a gaseous mixture and states that a specific gas type in a mixture exerts its own pressure; thus, the total pressure exerted by a mixture of gases is the sum of the partial pressures of the gases in the mixture.

Partial Pressures of Atmospheric Gases				
Gas	Percent of total composition	Partial pressure (mm Hg)		
Nitrogen (N ₂)	78.6	597.4		
Oxygen (O ₂)	20.9	158.8		
Water (H ₂ O)	0.04	3.0		
Carbon dioxide (CO ₂)	0.004	0.3		
Others	0.0006	0.5		
Total composition/total atmospheric pressure	100%	760.0		

Partial and Total Pressures of a Gas



Partial pressure is the force exerted by a gas. The sum of the partial pressures of all the gases in a mixture equals the total pressure.

Partial pressure is extremely important in predicting the movement of gases. Recall that gases tend to equalize their pressure in two regions that are connected. A gas will move from an area where its partial pressure is higher to an area where its partial pressure is lower. In addition, the greater the partial pressure difference between the two areas, the more rapid is the movement of gases.

Solubility of Gases in Liquids

Henry's law describes the behavior of gases when they come into contact with a liquid, such as blood. Henry's law states that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas. The greater the partial pressure of the gas, the greater the number of gas molecules that will dissolve in the liquid. The concentration of the gas in a liquid is also dependent on the solubility of the gas in the liquid. For example, although nitrogen is present in the atmosphere, very little nitrogen dissolves into the blood, because the solubility of nitrogen in blood is very low. The exception to this occurs in scuba divers; the composition of the compressed air that divers breathe causes nitrogen to have a higher partial pressure than normal, causing it to dissolve in the blood in greater amounts than normal. Too much nitrogen in the bloodstream results in a

serious condition that can be fatal if not corrected. Gas molecules establish an equilibrium between those molecules dissolved in liquid and those in air.

The composition of air in the atmosphere and in the alveoli differs. In both cases, the relative concentration of gases is nitrogen > oxygen > water vapor > carbon dioxide. The amount of water vapor present in alveolar air is greater than that in atmospheric air ([link]). Recall that the respiratory system works to humidify incoming air, thereby causing the air present in the alveoli to have a greater amount of water vapor than atmospheric air. In addition, alveolar air contains a greater amount of carbon dioxide and less oxygen than atmospheric air. This is no surprise, as gas exchange removes oxygen from and adds carbon dioxide to alveolar air. Both deep and forced breathing cause the alveolar air composition to be changed more rapidly than during quiet breathing. As a result, the partial pressures of oxygen and carbon dioxide change, affecting the diffusion process that moves these materials across the membrane. This will cause oxygen to enter and carbon dioxide to leave the blood more quickly.

Composition and Partial Pressures of Alveolar Air				
Gas	Percent of total composition	Partial pressure (mm Hg)		
Nitrogen (N ₂)	74.9	569		
Oxygen (O ₂)	13.7	104		
Water (H ₂ O)	6.2	40		
Carbon dioxide (CO ₂)	5.2	47		

Composition and Partial Pressures of Alveolar Air			
Gas	Percent of total composition	Partial pressure (mm Hg)	
Total composition/total alveolar pressure	100%	760.0	

Note:



Watch this video to learn more about Henry's law.

Ventilation and Perfusion

Two important aspects of gas exchange in the lung are ventilation and perfusion. **Ventilation** is the movement of air into and out of the lungs, and perfusion is the flow of blood in the pulmonary capillaries. For gas exchange to be efficient, the volumes involved in ventilation and perfusion should be compatible. However, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion to be imbalanced.

The partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of the oxygenated pulmonary venous blood is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In

contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane. The body has mechanisms that counteract this problem. In cases when ventilation is not sufficient for an alveolus, the body redirects blood flow to alveoli that are receiving sufficient ventilation. This is achieved by constricting the pulmonary arterioles that serves the dysfunctional alveolus, which redirects blood to other alveoli that have sufficient ventilation. At the same time, the pulmonary arterioles that serve alveoli receiving sufficient ventilation vasodilate, which brings in greater blood flow. Factors such as carbon dioxide, oxygen, and pH levels can all serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli.

Ventilation is regulated by the diameter of the airways, whereas perfusion is regulated by the diameter of the blood vessels. The diameter of the bronchioles is sensitive to the partial pressure of carbon dioxide in the alveoli. A greater partial pressure of carbon dioxide in the alveoli causes the bronchioles to increase their diameter as will a decreased level of oxygen in the blood supply, allowing carbon dioxide to be exhaled from the body at a greater rate. As mentioned above, a greater partial pressure of oxygen in the alveoli causes the pulmonary arterioles to dilate, increasing blood flow.

Gas Exchange

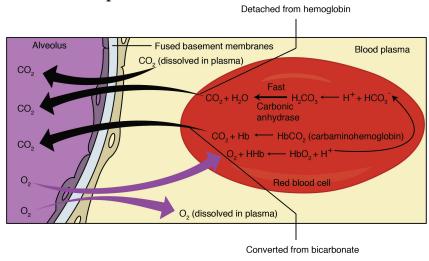
Gas exchange occurs at two sites in the body: in the lungs, where oxygen is picked up and carbon dioxide is released at the respiratory membrane, and at the tissues, where oxygen is released and carbon dioxide is picked up. External respiration is the exchange of gases with the external environment, and occurs in the alveoli of the lungs. Internal respiration is the exchange of gases with the internal environment, and occurs in the tissues. The actual exchange of gases occurs due to simple diffusion. Energy is not required to move oxygen or carbon dioxide across membranes. Instead, these gases follow pressure gradients that allow them to diffuse. The anatomy of the lung maximizes the diffusion of gases: The respiratory membrane is highly permeable to gases; the respiratory and blood capillary membranes are very thin; and there is a large surface area throughout the lungs.

External Respiration

The pulmonary artery carries deoxygenated blood into the lungs from the heart, where it branches and eventually becomes the capillary network composed of pulmonary capillaries. These pulmonary capillaries create the respiratory membrane with the alveoli ([link]). As the blood is pumped through this capillary network, gas exchange occurs. Although a small amount of the oxygen is able to dissolve directly into plasma from the alveoli, most of the oxygen is picked up by erythrocytes (red blood cells) and binds to a protein called hemoglobin, a process described later in this chapter. Oxygenated hemoglobin is red, causing the overall appearance of bright red oxygenated blood, which returns to the heart through the pulmonary veins. Carbon dioxide is released in the opposite direction of oxygen, from the blood to the alveoli. Some of the carbon dioxide is returned on hemoglobin, but can also be dissolved in plasma or is present as a converted form, also explained in greater detail later in this chapter.

External respiration occurs as a function of partial pressure differences in oxygen and carbon dioxide between the alveoli and the blood in the pulmonary capillaries.

External Respiration



In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus. Hb = Hemoglobin; H_2CO_3 = carbonic acid; HCO_3

Although the solubility of oxygen in blood is not high, there is a drastic difference in the partial pressure of oxygen in the alveoli versus in the blood of the pulmonary capillaries. This difference is about 64 mm Hg. The partial pressure of oxygen in the alveoli is about 104 mm Hg, whereas its partial pressure in the blood of the capillary is about 40 mm Hg. This large difference in partial pressure creates a very strong pressure gradient that causes oxygen to rapidly cross the respiratory membrane from the alveoli into the blood.

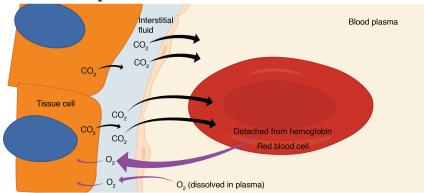
The partial pressure of carbon dioxide is also different between the alveolar air and the blood of the capillary. However, the partial pressure difference is less than that of oxygen, about 5 mm Hg. The partial pressure of carbon dioxide in the blood of the capillary is about 45 mm Hg, whereas its partial pressure in the alveoli is about 40 mm Hg. However, the solubility of carbon dioxide is much greater than that of oxygen—by a factor of about 20—in both blood and alveolar fluids. As a result, the relative concentrations of oxygen and carbon dioxide that diffuse across the respiratory membrane are similar.

Internal Respiration

Internal respiration is gas exchange that occurs at the level of body tissues ([link]). Similar to external respiration, internal respiration also occurs as simple diffusion due to a partial pressure gradient. However, the partial pressure gradients are opposite of those present at the respiratory membrane. The partial pressure of oxygen in tissues is low, about 40 mm Hg, because oxygen is continuously used for cellular respiration. In contrast, the partial pressure of oxygen in the blood is about 100 mm Hg. This creates a pressure gradient that causes oxygen to dissociate from hemoglobin, diffuse out of the blood, cross the interstitial space, and enter the tissue. Hemoglobin that has little oxygen bound to it loses much of its brightness, so that blood returning to the heart is more burgundy in color.

Considering that cellular respiration continuously produces carbon dioxide, the partial pressure of carbon dioxide is lower in the blood than it is in the tissue, causing carbon dioxide to diffuse out of the tissue, cross the interstitial fluid, and enter the blood. It is then carried back to the lungs either bound to hemoglobin, dissolved in plasma, or in a converted form. By the time blood returns to the heart, the partial pressure of oxygen has returned to about 40 mm Hg, and the partial pressure of carbon dioxide has returned to about 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.

Internal Respiration



Oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary.

Note:

Everyday Connection

Hyperbaric Chamber Treatment

A type of device used in some areas of medicine that exploits the behavior of gases is hyperbaric chamber treatment. A hyperbaric chamber is a unit that can be sealed and expose a patient to either 100 percent oxygen with increased pressure or a mixture of gases that includes a higher concentration of oxygen than normal atmospheric air, also at a higher partial pressure than the atmosphere. There are two major types of chambers: monoplace and multiplace. Monoplace chambers are typically

for one patient, and the staff tending to the patient observes the patient from outside of the chamber ([link]). Some facilities have special monoplace hyperbaric chambers that allow multiple patients to be treated at once, usually in a sitting or reclining position, to help ease feelings of isolation or claustrophobia. Multiplace chambers are large enough for multiple patients to be treated at one time, and the staff attending these patients is present inside the chamber. In a multiplace chamber, patients are often treated with air via a mask or hood, and the chamber is pressurized.

Hyperbaric Chamber



(credit: "komunews"/flickr.com)

Hyperbaric chamber treatment is based on the behavior of gases. As you recall, gases move from a region of higher partial pressure to a region of lower partial pressure. In a hyperbaric chamber, the atmospheric pressure is increased, causing a greater amount of oxygen than normal to diffuse into the bloodstream of the patient. Hyperbaric chamber therapy is used to treat a variety of medical problems, such as wound and graft healing, anaerobic bacterial infections, and carbon monoxide poisoning. Exposure to and poisoning by carbon monoxide is difficult to reverse, because hemoglobin's affinity for carbon monoxide is much stronger than its affinity for oxygen, causing carbon monoxide to replace oxygen in the blood. Hyperbaric chamber therapy can treat carbon monoxide poisoning,

because the increased atmospheric pressure causes more oxygen to diffuse into the bloodstream. At this increased pressure and increased concentration of oxygen, carbon monoxide is displaced from hemoglobin. Another example is the treatment of anaerobic bacterial infections, which are created by bacteria that cannot or prefer not to live in the presence of oxygen. An increase in blood and tissue levels of oxygen helps to kill the anaerobic bacteria that are responsible for the infection, as oxygen is toxic to anaerobic bacteria. For wounds and grafts, the chamber stimulates the healing process by increasing energy production needed for repair. Increasing oxygen transport allows cells to ramp up cellular respiration and thus ATP production, the energy needed to build new structures.

Chapter Review

The behavior of gases can be explained by the principles of Dalton's law and Henry's law, both of which describe aspects of gas exchange. Dalton's law states that each specific gas in a mixture of gases exerts force (its partial pressure) independently of the other gases in the mixture. Henry's law states that the amount of a specific gas that dissolves in a liquid is a function of its partial pressure. The greater the partial pressure of a gas, the more of that gas will dissolve in a liquid, as the gas moves toward equilibrium. Gas molecules move down a pressure gradient; in other words, gas moves from a region of high pressure to a region of low pressure. The partial pressure of oxygen is high in the alveoli and low in the blood of the pulmonary capillaries. As a result, oxygen diffuses across the respiratory membrane from the alveoli into the blood. In contrast, the partial pressure of carbon dioxide is high in the pulmonary capillaries and low in the alveoli. Therefore, carbon dioxide diffuses across the respiratory membrane from the blood into the alveoli. The amount of oxygen and carbon dioxide that diffuses across the respiratory membrane is similar.

Ventilation is the process that moves air into and out of the alveoli, and perfusion affects the flow of blood in the capillaries. Both are important in gas exchange, as ventilation must be sufficient to create a high partial pressure of oxygen in the alveoli. If ventilation is insufficient and the partial

pressure of oxygen drops in the alveolar air, the capillary is constricted and blood flow is redirected to alveoli with sufficient ventilation. External respiration refers to gas exchange that occurs in the alveoli, whereas internal respiration refers to gas exchange that occurs in the tissue. Both are driven by partial pressure differences.

Glossary

Dalton's law

statement of the principle that a specific gas type in a mixture exerts its own pressure, as if that specific gas type was not part of a mixture of gases

external respiration

gas exchange that occurs in the alveoli

Henry's law

statement of the principle that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas

internal respiration

gas exchange that occurs at the level of body tissues

partial pressure

force exerted by each gas in a mixture of gases

total pressure

sum of all the partial pressures of a gaseous mixture

ventilation

movement of air into and out of the lungs; consists of inspiration and expiration

OU Human Physiology: Transport of Gases By the end of this section, you will be able to:

- Describe how oxygen is transported via the plasma
- Describe the structure and function of hemoglobin
- Explain how the partial pressure of oxygen plays a major role in determining the degree of binding of oxygen to heme
- Describe the mechanisms for carbon dioxide transport in the blood

The other major activity in the lungs is the process of respiration, the process of gas exchange. The function of respiration is to provide oxygen for use by body cells during cellular respiration and to eliminate carbon dioxide, a waste product of cellular respiration, from the body. In order for the exchange of oxygen and carbon dioxide to occur, both gases must be transported between the external and internal respiration sites. Although carbon dioxide is more soluble than oxygen in blood, both gases require a specialized transport system for the majority of the gas molecules to be moved between the lungs and other tissues.

Oxygen Transport in the Blood

Even though oxygen is transported via the blood, you may recall that oxygen is not very soluble in liquids. A small amount of oxygen does dissolve in the blood and is transported in the bloodstream, but it is only about 1.5% of the total amount. The majority of oxygen molecules are carried from the lungs to the body's tissues by a specialized transport system, which relies on the erythrocyte—the red blood cell. Erythrocytes contain a metalloprotein, hemoglobin, which serves to bind oxygen molecules to the erythrocyte ([link]). Hemoglobin consists of four subunits, each containing a globin (globular protein consisting of two alpha and two beta chains). Each subunit contains a heme groups. The heme group is named as such because it contains iron (Fe). Each heme group has only one iron molecule and each iron molecule can only bind one molecule of oxygen. As oxygen diffuses across the respiratory membrane from the alveolus to the capillary, it also diffuses into the red blood cell and is bound by hemoglobin. The following reversible chemical reaction describes the production of the final product, **oxyhemoglobin** (Hb–O₂), which is formed

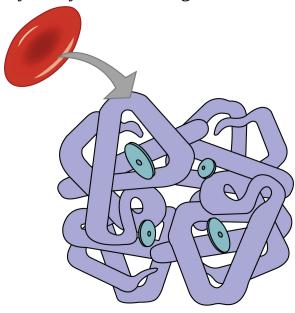
when oxygen binds to hemoglobin. Oxyhemoglobin is a bright red-colored molecule that contributes to the bright red color of oxygenated blood.

Equation:

$$\mathrm{Hb} + \mathrm{O}_2 \leftrightarrow \mathrm{Hb} - \mathrm{O}_2$$

In this formula, Hb represents reduced hemoglobin, that is, hemoglobin that does not have oxygen bound to it. There are multiple factors involved in how readily heme binds to and dissociates from oxygen, which will be discussed in the subsequent sections.

Erythrocyte and Hemoglobin



Hemoglobin consists of four subunits, each of which contains one molecule of iron.

Function of Hemoglobin

Hemoglobin is composed of subunits, a protein structure that is referred to as a quaternary structure. Each of the four subunits that make up

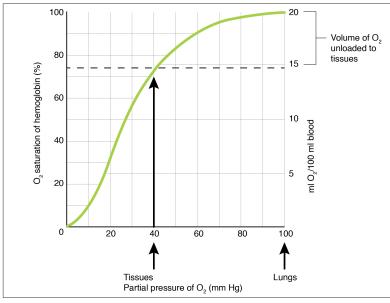
hemoglobin is arranged in a ring-like fashion, with an iron atom covalently bound to the heme in the center of each subunit. Binding of the first oxygen molecule causes a conformational change in hemoglobin that allows the second molecule of oxygen to bind more readily. As each molecule of oxygen is bound, it further facilitates the binding of the next molecule, until all four heme sites are occupied by oxygen. The opposite occurs as well: After the first oxygen molecule dissociates and is "dropped off" at the tissues, the next oxygen molecule dissociates more readily. When all four heme sites are occupied, the hemoglobin is said to be saturated. When one to three heme sites are occupied, the hemoglobin is said to be partially saturated. Therefore, when considering the blood as a whole, the percent of the available heme units that are bound to oxygen at a given time is called hemoglobin saturation. Hemoglobin saturation of 100 percent means that every heme unit in all of the erythrocytes of the body is bound to oxygen. In a healthy individual with normal hemoglobin levels, hemoglobin saturation generally ranges from 95 percent to 99 percent.

Oxygen Dissociation from Hemoglobin

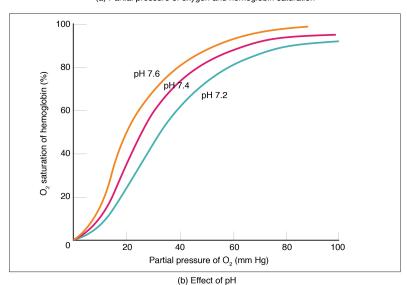
Partial pressure is an important aspect of the binding of oxygen to and disassociation from heme. An **oxygen–hemoglobin dissociation curve** is a graph that describes the relationship of partial pressure to the binding of oxygen to heme and its subsequent dissociation from heme ([link]). Remember that gases travel from an area of higher partial pressure to an area of lower partial pressure. In addition, the affinity of an oxygen molecule for heme increases as more oxygen molecules are bound. Therefore, in the oxygen—hemoglobin saturation curve, as the partial pressure of oxygen increases, a proportionately greater number of oxygen molecules are bound by heme. Not surprisingly, the oxygen–hemoglobin saturation/dissociation curve also shows that the lower the partial pressure of oxygen, the fewer oxygen molecules are bound to heme. As a result, the partial pressure of oxygen plays a major role in determining the degree of binding of oxygen to heme at the site of the respiratory membrane, as well as the degree of dissociation of oxygen from heme at the site of body tissues.

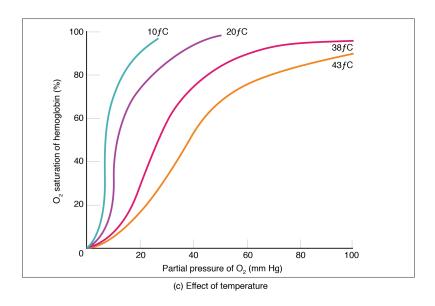
Oxygen-Hemoglobin Dissociation and Effects of pH and Temperature

These three graphs show (a) the relationship between the partial pressure of oxygen and hemoglobin saturation, (b) the effect of pH on the oxygen—hemoglobin dissociation curve, and (c) the effect of temperature on the oxygen—hemoglobin dissociation curve.



(a) Partial pressure of oxygen and hemoglobin saturation





The mechanisms behind the oxygen–hemoglobin saturation/dissociation curve also serve as automatic control mechanisms that regulate how much oxygen is delivered to different tissues throughout the body. This is important because some tissues have a higher metabolic rate than others. Highly active tissues, such as muscle, rapidly use oxygen to produce ATP, lowering the partial pressure of oxygen in the tissue to about 20 mm Hg. The partial pressure of oxygen inside capillaries is about 100 mm Hg, so the difference between the two becomes quite high, about 80 mm Hg. As a result, a greater number of oxygen molecules dissociate from hemoglobin and enter the tissues. The reverse is true of tissues, such as adipose (body fat), which have lower metabolic rates. Because less oxygen is used by these cells, the partial pressure of oxygen within such tissues remains relatively high, resulting in fewer oxygen molecules dissociating from hemoglobin and entering the tissue interstitial fluid. Although venous blood is said to be deoxygenated, some oxygen is still bound to hemoglobin in its red blood cells. This provides an oxygen reserve that can be used when tissues suddenly demand more oxygen.

Factors other than partial pressure also affect the oxygen—hemoglobin saturation/dissociation curve. For example, a higher temperature promotes hemoglobin and oxygen to dissociate faster, whereas a lower temperature inhibits dissociation (see [link], middle). However, the human body tightly regulates temperature, so this factor may not affect gas exchange throughout the body. The exception to this is in highly active tissues, which

may release a larger amount of energy than is given off as heat. As a result, oxygen readily dissociates from hemoglobin, which is a mechanism that helps to provide active tissues with more oxygen.

Certain hormones, such as androgens, epinephrine, thyroid hormones, and growth hormone, can affect the oxygen—hemoglobin saturation/disassociation curve by stimulating the production of a compound called 2,3-bisphosphoglycerate (BPG) by erythrocytes. BPG is a byproduct of glycolysis. Because erythrocytes do not contain mitochondria, glycolysis is the sole method by which these cells produce ATP. BPG promotes the disassociation of oxygen from hemoglobin. Therefore, the greater the concentration of BPG, the more readily oxygen dissociates from hemoglobin, despite its partial pressure.

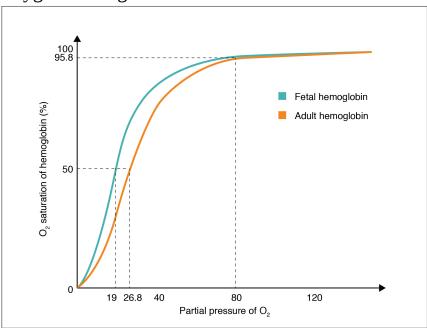
The pH of the blood is another factor that influences the oxygen—hemoglobin saturation/dissociation curve (see [link]). The **Bohr effect** is a phenomenon that arises from the relationship between pH and oxygen's affinity for hemoglobin: A lower, more acidic pH promotes oxygen dissociation from hemoglobin. In contrast, a higher, or more basic, pH inhibits oxygen dissociation from hemoglobin. The greater the amount of carbon dioxide in the blood, the more molecules that must be converted, which in turn generates hydrogen ions and thus lowers blood pH. Furthermore, blood pH may become more acidic when certain byproducts of cell metabolism, such as lactic acid, carbonic acid, and carbon dioxide, are released into the bloodstream.

Hemoglobin of the Fetus

The fetus has its own circulation with its own erythrocytes; however, it is dependent on the mother for oxygen. Blood is supplied to the fetus by way of the umbilical cord, which is connected to the placenta and separated from maternal blood by the chorion. The mechanism of gas exchange at the chorion is similar to gas exchange at the respiratory membrane. However, the partial pressure of oxygen is lower in the maternal blood in the placenta, at about 35 to 50 mm Hg, than it is in maternal arterial blood. The difference in partial pressures between maternal and fetal blood is not large,

as the partial pressure of oxygen in fetal blood at the placenta is about 20 mm Hg. Therefore, there is not as much diffusion of oxygen into the fetal blood supply. The fetus' hemoglobin overcomes this problem by having a greater affinity for oxygen than maternal hemoglobin ([link]). Both fetal and adult hemoglobin have four subunits, but two of the subunits of fetal hemoglobin have a different structure that causes fetal hemoglobin to have a greater affinity for oxygen than does adult hemoglobin.

Oxygen-Hemoglobin Dissociation Curves in Fetus and Adult

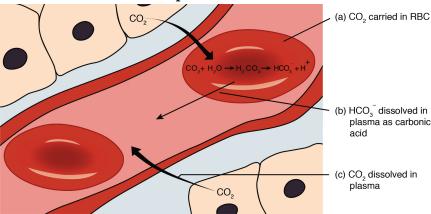


Fetal hemoglobin has a greater affinity for oxygen than does adult hemoglobin.

Carbon Dioxide Transport in the Blood

Carbon dioxide is transported by three major mechanisms. The first mechanism of carbon dioxide transport is by blood plasma, as some carbon dioxide molecules dissolve in the blood. The second mechanism is transport in the form of bicarbonate (HCO_3^-), which also dissolves in plasma. The third mechanism of carbon dioxide transport is similar to the transport of oxygen by erythrocytes ([link]).

Carbon Dioxide Transport



Carbon dioxide is transported by three different methods: (a) in erythrocytes; (b) after forming carbonic acid, which is dissolved in plasma; (c) and in plasma. RBC = red blood cell; H_2CO_3 = carbonic acid; HCO_3 ⁻ = bicarbonate

Dissolved Carbon Dioxide

Although carbon dioxide is not considered to be highly soluble in blood, a small fraction—about 7 to 10 percent—of the carbon dioxide that diffuses into the blood from the tissues dissolves in plasma. The dissolved carbon dioxide then travels in the bloodstream and when the blood reaches the pulmonary capillaries, the dissolved carbon dioxide diffuses across the respiratory membrane into the alveoli, where it is then exhaled during pulmonary ventilation.

Bicarbonate Buffer

A large fraction—about 70 percent—of the carbon dioxide molecules that diffuse into the blood is transported to the lungs as bicarbonate. Most bicarbonate is produced in erythrocytes after carbon dioxide diffuses into

the capillaries, and subsequently into red blood cells. **Carbonic anhydrase (CA)** causes carbon dioxide and water to form carbonic acid (H_2CO_3) , which dissociates into two ions: bicarbonate (HCO_3^-) and hydrogen (H^+) . The following formula depicts this reaction:

Equation:

$$\mathrm{CO_2} + \mathrm{H_2O} \overset{\mathrm{CA}}{\leftrightarrow} \mathrm{H_2CO_3} \leftrightarrow \mathrm{H^+} + \mathrm{HCO_{3-}}$$

Bicarbonate tends to build up in the erythrocytes, so that there is a greater concentration of bicarbonate in the erythrocytes than in the surrounding blood plasma. As a result, some of the bicarbonate will leave the erythrocytes and move down its concentration gradient into the plasma in exchange for chloride (Cl⁻) ions. This phenomenon is referred to as the **chloride shift** and occurs because by exchanging one negative ion for another negative ion, neither the electrical charge of the erythrocytes nor that of the blood is altered.

At the pulmonary capillaries, the chemical reaction that produced bicarbonate (shown above) is reversed, and carbon dioxide and water are the products. Much of the bicarbonate in the plasma re-enters the erythrocytes in exchange for chloride ions. Hydrogen ions and bicarbonate ions join to form carbonic acid, which is converted into carbon dioxide and water by carbonic anhydrase. Carbon dioxide diffuses out of the erythrocytes and into the plasma, where it can further diffuse across the respiratory membrane into the alveoli to be exhaled during pulmonary ventilation.

Carbaminohemoglobin

About 20 percent of carbon dioxide is bound by hemoglobin and is transported to the lungs. Carbon dioxide does not bind to iron as oxygen does; instead, carbon dioxide binds amino acid moieties on the globin portions of hemoglobin to form **carbaminohemoglobin**, which forms when hemoglobin and carbon dioxide bind. When hemoglobin is not transporting oxygen, it tends to have a bluish-purple tone to it, creating the darker

maroon color typical of deoxygenated blood. The following formula depicts this reversible reaction:

Equation:

$$CO_2 + Hb \leftrightarrow HbCO_2$$

Similar to the transport of oxygen by heme, the binding and dissociation of carbon dioxide to and from hemoglobin is dependent on the partial pressure of carbon dioxide. Because carbon dioxide is released from the lungs, blood that leaves the lungs and reaches body tissues has a lower partial pressure of carbon dioxide than is found in the tissues. As a result, carbon dioxide leaves the tissues because of its higher partial pressure, enters the blood, and then moves into red blood cells, binding to hemoglobin. In contrast, in the pulmonary capillaries, the partial pressure of carbon dioxide is high compared to within the alveoli. As a result, carbon dioxide dissociates readily from hemoglobin and diffuses across the respiratory membrane into the air.

In addition to the partial pressure of carbon dioxide, the oxygen saturation of hemoglobin and the partial pressure of oxygen in the blood also influence the affinity of hemoglobin for carbon dioxide. The **Haldane effect** is a phenomenon that arises from the relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide. Hemoglobin that is saturated with oxygen does not readily bind carbon dioxide. However, when oxygen is not bound to heme and the partial pressure of oxygen is low, hemoglobin readily binds to carbon dioxide.

Note: | Image: | Ima

Watch this <u>video</u> to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

Chapter Review

Oxygen is primarily transported through the blood by erythrocytes. These cells contain hemoglobin, which is composed of four subunits with a ringlike structure. Each subunit contains one atom of iron bound to a molecule of heme. Heme binds oxygen so that each hemoglobin molecule can bind up to four oxygen molecules. When all of the heme units in the blood are bound to oxygen, hemoglobin is considered to be saturated. Hemoglobin is partially saturated when only some heme units are bound to oxygen. An oxygen-hemoglobin saturation/dissociation curve is a common way to depict the relationship of how easily oxygen binds to or dissociates from hemoglobin as a function of the partial pressure of oxygen. As the partial pressure of oxygen increases, the more readily hemoglobin binds to oxygen. At the same time, once one molecule of oxygen is bound by hemoglobin, additional oxygen molecules more readily bind to hemoglobin. Other factors such as temperature, pH, the partial pressure of carbon dioxide, and the concentration of 2,3-bisphosphoglycerate can enhance or inhibit the binding of hemoglobin and oxygen as well. Fetal hemoglobin has a different structure than adult hemoglobin, which results in fetal hemoglobin having a greater affinity for oxygen than adult hemoglobin.

Carbon dioxide is transported in blood by three different mechanisms: as dissolved carbon dioxide, as bicarbonate, or as carbaminohemoglobin. A small portion of carbon dioxide remains. The largest amount of transported carbon dioxide is as bicarbonate, formed in erythrocytes. For this conversion, carbon dioxide is combined with water with the aid of an enzyme called carbonic anhydrase. This combination forms carbonic acid, which spontaneously dissociates into bicarbonate and hydrogen ions. As bicarbonate builds up in erythrocytes, it is moved across the membrane into the plasma in exchange for chloride ions by a mechanism called the chloride shift. At the pulmonary capillaries, bicarbonate re-enters

erythrocytes in exchange for chloride ions, and the reaction with carbonic anhydrase is reversed, recreating carbon dioxide and water. Carbon dioxide then diffuses out of the erythrocyte and across the respiratory membrane into the air. An intermediate amount of carbon dioxide binds directly to hemoglobin to form carbaminohemoglobin. The partial pressures of carbon dioxide and oxygen, as well as the oxygen saturation of hemoglobin, influence how readily hemoglobin binds carbon dioxide. The less saturated hemoglobin is and the lower the partial pressure of oxygen in the blood is, the more readily hemoglobin binds to carbon dioxide. This is an example of the Haldane effect.

Glossary

Bohr effect

relationship between blood pH and oxygen dissociation from hemoglobin

carbaminohemoglobin

bound form of hemoglobin and carbon dioxide

carbonic anhydrase (CA)

enzyme that catalyzes the reaction that causes carbon dioxide and water to form carbonic acid

chloride shift

facilitated diffusion that exchanges bicarbonate (HCO₃⁻) with chloride (Cl⁻) ions

Haldane effect

relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide

oxyhemoglobin

(Hb–O₂) bound form of hemoglobin and oxygen

oxygen-hemoglobin dissociation curve

graph that describes the relationship of partial pressure to the binding and disassociation of oxygen to and from heme

OU Human Physiology: Modifications in Respiratory Functions

At rest, the respiratory system performs its functions at a constant, rhythmic pace, as regulated by the respiratory centers of the brain. At this pace, ventilation provides sufficient oxygen to all the tissues of the body. However, there are times that the respiratory system must alter the pace of its functions in order to accommodate the oxygen demands of the body.

Hyperpnea

Hyperpnea is an increased depth and rate of ventilation to meet an increase in oxygen demand as might be seen in exercise or disease, particularly diseases that target the respiratory or digestive tracts. This does not significantly alter blood oxygen or carbon dioxide levels, but merely increases the depth and rate of ventilation to meet the demand of the cells. In contrast, hyperventilation is an increased ventilation rate that is independent of the cellular oxygen needs and leads to abnormally low blood carbon dioxide levels and high (alkaline) blood pH.

Interestingly, exercise does not cause hyperpnea as one might think. Muscles that perform work during exercise do increase their demand for oxygen, stimulating an increase in ventilation. However, hyperpnea during exercise appears to occur before a drop in oxygen levels within the muscles can occur. Therefore, hyperpnea must be driven by other mechanisms, either instead of or in addition to a drop in oxygen levels. The exact mechanisms behind exercise hyperpnea are not well understood, and some hypotheses are somewhat controversial. However, in addition to low oxygen, high carbon dioxide, and low pH levels, there appears to be a complex interplay of factors related to the nervous system and the respiratory centers of the brain.

First, a conscious decision to partake in exercise, or another form of physical exertion, results in a psychological stimulus that may trigger the respiratory centers of the brain to increase ventilation. In addition, the respiratory centers of the brain may be stimulated through the activation of motor neurons that innervate muscle groups that are involved in the physical activity. Finally, physical exertion stimulates proprioceptors, which

are receptors located within the muscles, joints, and tendons, which sense movement and stretching; proprioceptors thus create a stimulus that may also trigger the respiratory centers of the brain. These neural factors are consistent with the sudden increase in ventilation that is observed immediately as exercise begins. Because the respiratory centers are stimulated by psychological, motor neuron, and proprioceptor inputs throughout exercise, the fact that there is also a sudden decrease in ventilation immediately after the exercise ends when these neural stimuli cease, further supports the idea that they are involved in triggering the changes of ventilation.

High Altitude Effects

An increase in altitude results in a decrease in atmospheric pressure. Although the proportion of oxygen relative to gases in the atmosphere remains at 21 percent, its partial pressure decreases ([link]). As a result, it is more difficult for a body to achieve the same level of oxygen saturation at high altitude than at low altitude, due to lower atmospheric pressure. In fact, hemoglobin saturation is lower at high altitudes compared to hemoglobin saturation at sea level. For example, hemoglobin saturation is about 67 percent at 19,000 feet above sea level, whereas it reaches about 98 percent at sea level.

Partial Pressure of Oxygen at Different Altitudes					
Example location	Altitude (feet above sea level)	Atmospheric pressure (mm Hg)	Partial pressure of oxygen (mm Hg)		

Partial Pressure of Oxygen at Different Altitudes				
Example location	Altitude (feet above sea level)	Atmospheric pressure (mm Hg)	Partial pressure of oxygen (mm Hg)	
New York City, New York	0	760	159	
Boulder, Colorado	5000	632	133	
Aspen, Colorado	8000	565	118	
Pike's Peak, Colorado	14,000	447	94	
Denali (Mt. McKinley), Alaska	20,000	350	73	
Mt. Everest, Tibet	29,000	260	54	

As you recall, partial pressure is extremely important in determining how much gas can cross the respiratory membrane and enter the blood of the pulmonary capillaries. A lower partial pressure of oxygen means that there is a smaller difference in partial pressures between the alveoli and the blood, so less oxygen crosses the respiratory membrane. As a result, fewer oxygen molecules are bound by hemoglobin. Despite this, the tissues of the body still receive a sufficient amount of oxygen during rest at high altitudes. This is due to two major mechanisms. First, the number of oxygen molecules that enter the tissue from the blood is nearly equal between sea

level and high altitudes. At sea level, hemoglobin saturation is higher, but only a quarter of the oxygen molecules are actually released into the tissue. At high altitudes, a greater proportion of molecules of oxygen are released into the tissues. Secondly, at high altitudes, a greater amount of BPG is produced by erythrocytes, which enhances the dissociation of oxygen from hemoglobin. Physical exertion, such as skiing or hiking, can lead to altitude sickness due to the low amount of oxygen reserves in the blood at high altitudes. At sea level, there is a large amount of oxygen reserve in venous blood (even though venous blood is thought of as "deoxygenated") from which the muscles can draw during physical exertion. Because the oxygen saturation is much lower at higher altitudes, this venous reserve is small, resulting in pathological symptoms of low blood oxygen levels. You may have heard that it is important to drink more water when traveling at higher altitudes than you are accustomed to. This is because your body will increase micturition (urination) at high altitudes to counteract the effects of lower oxygen levels. By removing fluids, blood plasma levels drop but not the total number of erythrocytes. In this way, the overall concentration of erythrocytes in the blood increases, which helps tissues obtain the oxygen they need.

Acute mountain sickness (AMS), or altitude sickness, is a condition that results from acute exposure to high altitudes due to a low partial pressure of oxygen at high altitudes. AMS typically can occur at 2400 meters (8000 feet) above sea level. AMS is a result of low blood oxygen levels, as the body has acute difficulty adjusting to the low partial pressure of oxygen. In serious cases, AMS can cause pulmonary or cerebral edema. Symptoms of AMS include nausea, vomiting, fatigue, lightheadedness, drowsiness, feeling disoriented, increased pulse, and nosebleeds. The only treatment for AMS is descending to a lower altitude; however, pharmacologic treatments and supplemental oxygen can improve symptoms. AMS can be prevented by slowly ascending to the desired altitude, allowing the body to acclimate, as well as maintaining proper hydration.

Acclimatization

Especially in situations where the ascent occurs too quickly, traveling to areas of high altitude can cause AMS. **Acclimatization** is the process of adjustment that the respiratory system makes due to chronic exposure to a high altitude. Over a period of time, the body adjusts to accommodate the lower partial pressure of oxygen. The low partial pressure of oxygen at high altitudes results in a lower oxygen saturation level of hemoglobin in the blood. In turn, the tissue levels of oxygen are also lower. As a result, the kidneys are stimulated to produce the hormone erythropoietin (EPO), which stimulates the production of erythrocytes, resulting in a greater number of circulating erythrocytes in an individual at a high altitude over a long period. With more red blood cells, there is more hemoglobin to help transport the available oxygen. Even though there is low saturation of each hemoglobin molecule, there will be more hemoglobin present, and therefore more oxygen in the blood. Over time, this allows the person to partake in physical exertion without developing AMS.

Chapter Review

Normally, the respiratory centers of the brain maintain a consistent, rhythmic breathing cycle. However, in certain cases, the respiratory system must adjust to situational changes in order to supply the body with sufficient oxygen. For example, exercise results in increased ventilation, and chronic exposure to a high altitude results in a greater number of circulating erythrocytes. Hyperpnea, an increase in the rate and depth of ventilation, appears to be a function of three neural mechanisms that include a psychological stimulus, motor neuron activation of skeletal muscles, and the activation of proprioceptors in the muscles, joints, and tendons. As a result, hyperpnea related to exercise is initiated when exercise begins, as opposed to when tissue oxygen demand actually increases.

In contrast, acute exposure to a high altitude, particularly during times of physical exertion, does result in low blood and tissue levels of oxygen. This change is caused by a low partial pressure of oxygen in the air, because the atmospheric pressure at high altitudes is lower than the atmospheric pressure at sea level. This can lead to a condition called acute mountain sickness (AMS) with symptoms that include headaches, disorientation, fatigue, nausea, and lightheadedness. Over a long period of time, a person's

body will adjust to the high altitude, a process called acclimatization. During acclimatization, the low tissue levels of oxygen will cause the kidneys to produce greater amounts of the hormone erythropoietin, which stimulates the production of erythrocytes. Increased levels of circulating erythrocytes provide an increased amount of hemoglobin that helps supply an individual with more oxygen, preventing the symptoms of AMS.

Glossary

acclimatization

process of adjustment that the respiratory system makes due to chronic exposure to high altitudes

acute mountain sickness (AMS)

condition that occurs a result of acute exposure to high altitude due to a low partial pressure of oxygen

hyperpnea

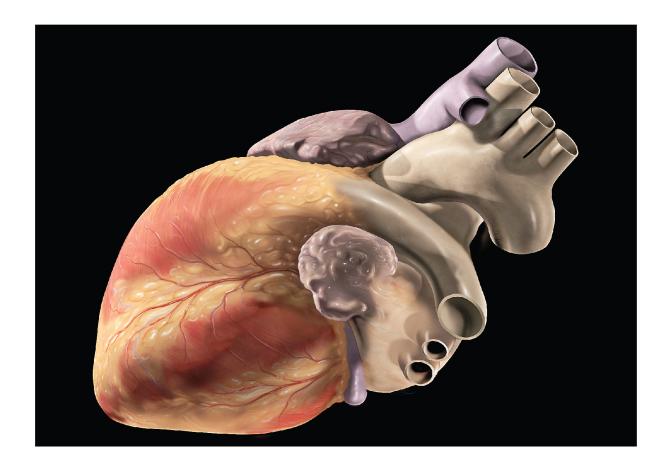
increased rate and depth of ventilation due to an increase in oxygen demand that does not significantly alter blood oxygen or carbon dioxide levels

hyperventilation

increased ventilation rate that leads to abnormally low blood carbon dioxide levels and high (alkaline) blood pH

OU Human Physiology: The Cardiovascular System Heart: Introduction class="introduction" Human Heart

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This artist's
conception
of the human
   heart
 suggests a
 powerful
engine—not
inappropriat
   e for a
 muscular
 pump that
 keeps the
   body
continually
  supplied
with blood.
  (credit:
 Patrick J.
  Lynch)
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Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the size, shape, and location of the human heart
- Describe the external and internal anatomy of the heart
- Describe the path of blood through the cardiac circuits
- Describe the structure of cardiac muscle
- Explain the cardiac conduction system and how it relates to the mechanical work of the cardiac contractile cells
- Compare and contrast pacemaker and cardiac action potentials
- Describe the process and purpose of an electrocardiogram
- Explain the cardiac cycle
- Create a flow chart illustrating how changes in heart rate and/or stroke volume alter cardiac output and how the body maintains homeostasis despite these changes

The cardiovascular system can be divided into three sections, the heart, the blood vessels, and the blood. In this chapter, you will explore the remarkable pump that propels the blood into the vessels. There is no single better word to describe the function of the heart other than "pump," since its contraction develops the pressure that ejects blood into the major vessels: the aorta and pulmonary trunk. From these vessels, the blood is distributed to the remainder of the body. Although the connotation of the term "pump" suggests a mechanical device made of steel and plastic, the anatomical structure is a living, sophisticated muscle. As you read this chapter, try to keep these twin concepts in mind: pump and muscle.

Although the term "heart" is an English word, cardiac (heart-related) terminology can be traced back to the Latin term, "kardia." Cardiology is the study of the heart, and cardiologists are the physicians who deal primarily with the heart.

OU Human Physiology: Heart Anatomy By the end of this section, you will be able to:

- Describe the location and position of the heart within the body cavity
- Describe the external and internal anatomy of the heart
- Identify the chambers and valves in the heart
- Compare and contrast the pulmonary and systemic circuits in human circulation
- Trace a single RBC from the right atrium through the pulmonary circuits and systemic circuits
- Identify major blood vessels in the pathway as well as chambers and valves in the heart
- Identify the tissue layers of the heart
- Relate the structure of the heart to its function as a pump
- Explain the importance of coronary circulation
- Trace a RBC to the coronary circulation and back to the heart
- Trace the pathway of oxygenated and deoxygenated blood through the chambers and valves of the heart
- Explain the cause of the 'lub' and 'dub' heart sounds

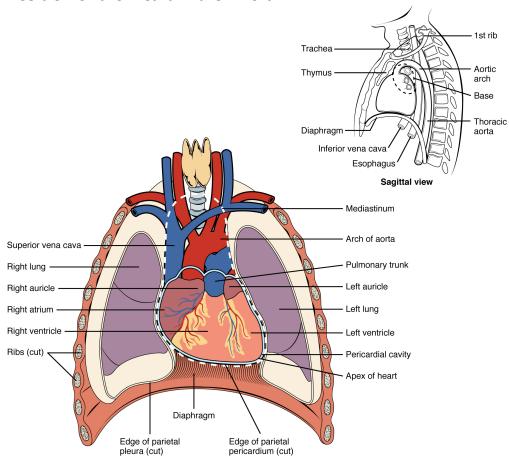
The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. [link] shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane

known as the pericardium, or pericardial sac, and sits in its own space called the **pericardial cavity**. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and pulmonary trunk, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in [link]. The inferior tip of the heart, the apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the **cardiac notch**.

Position of the Heart in the Thorax



The heart is located within the thoracic cavity, medially between the lungs in the mediastinum. It is about the size of a fist, is broad at the top, and tapers toward the base.

Note:

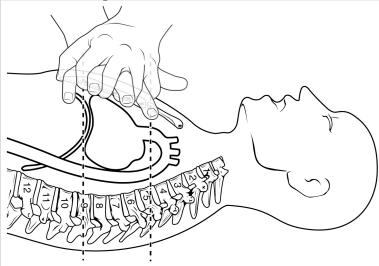
Everyday Connection **CPR**

The position of the heart in the torso between the vertebrae and sternum (see [link] for the position of the heart within the thorax) allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the line at T4 and T9 ([link]), it is possible to manually compress the blood within the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in "Staying Alive," recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, a version is available on www.youtube.com. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced healthcare professional.

When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a consequence that may prove fatal for the patient. Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the

American Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.

CPR Technique



If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.

Note:



Visit the American Heart Association <u>website</u> to help locate a course near your home in the United States. There are also many other national and regional heart associations that offer the same service, depending upon the location.

Shape and Size of the Heart

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex (see [link]). A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a welltrained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as **hypertrophic cardiomyopathy**. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

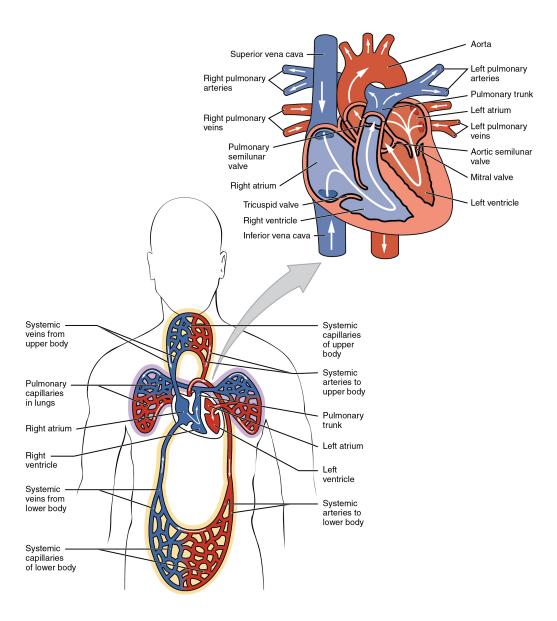
Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one **atrium** and one **ventricle**. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

There are two distinct but linked circuits in the human circulation called the pulmonary and systemic circuits. Although both circuits transport blood and everything it carries, we can initially view the circuits from the point of view of gases. The **pulmonary circuit** transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The **systemic circuit** transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

The right ventricle pumps deoxygenated blood into the **pulmonary trunk**, which leads toward the lungs and bifurcates into the left and right **pulmonary arteries.** These vessels in turn branch many times before reaching the **pulmonary capillaries**, where gas exchange occurs: Carbon dioxide exits the blood and oxygen enters. The pulmonary trunk arteries and their branches are the only arteries in the post-natal body that carry relatively deoxygenated blood. Highly oxygenated blood returning from the pulmonary capillaries in the lungs passes through a series of vessels that join together to form the **pulmonary veins**—the only post-natal veins in the body that carry highly oxygenated blood. The pulmonary veins conduct blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and on to the many branches of the systemic circuit. Eventually, these vessels will lead to the systemic capillaries, where exchange with the tissue fluid and cells of the body occurs. In this case, oxygen and nutrients exit the systemic capillaries to be used by the cells in their metabolic processes, and carbon dioxide and waste products will enter the blood.

The blood exiting the systemic capillaries is lower in oxygen concentration than when it entered. The capillaries will ultimately unite to form venules, joining to form ever-larger veins, eventually flowing into the two major systemic veins, the **superior vena cava** and the **inferior vena cava**, which return blood to the right atrium. The blood in the superior and inferior venae cavae flows into the right atrium, which pumps blood into the right ventricle. This process of blood circulation continues as long as the individual remains alive. Understanding the flow of blood through the pulmonary and systemic circuits is critical to all health professions ([link]). Dual System of the Human Blood Circulation



Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon

dioxide and wastes in), blood returns to the right atrium and the cycle is repeated.

Membranes, Surface Features, and Layers

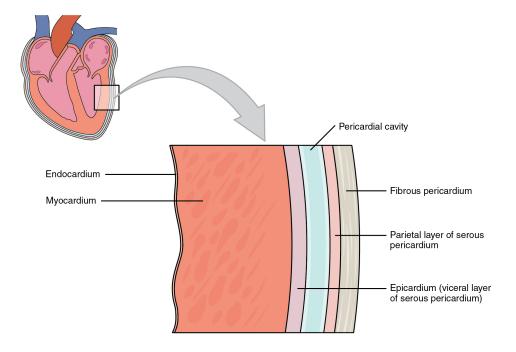
Our exploration of more in-depth heart structures begins by examining the membrane that surrounds the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.

Membranes

The membrane that directly surrounds the heart and defines the pericardial cavity is called the **pericardium** or **pericardial sac**. It also surrounds the "roots" of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as "around the heart," consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or **epicardium**, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a **mesothelium**, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts. [link] illustrates the pericardial membrane and the layers of the heart.

Pericardial Membranes and Layers of the Heart Wall



The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

Note:

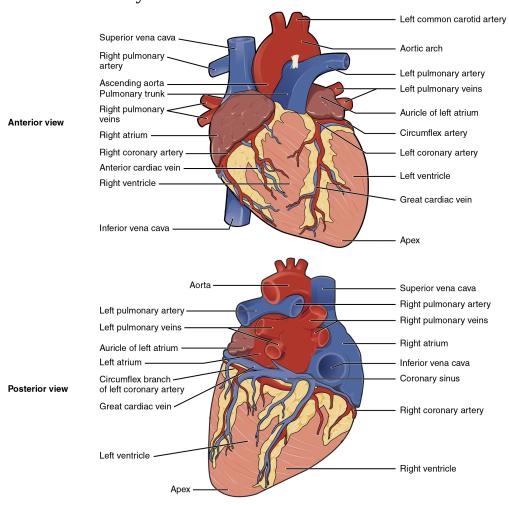
Disorders of the...

Heart: Cardiac Tamponade

If excess fluid builds within the pericardial space, it can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates within the pericardial cavity. In order to fill with blood for the next contraction, the heart must relax. However, the excess fluid in the pericardial cavity puts pressure on the heart and prevents full relaxation, so the chambers within the heart contain slightly less blood as they begin each heart cycle. Over time, less and less blood is ejected from the heart. If the fluid builds up slowly, as in hypothyroidism, the pericardial cavity may be able to expand gradually to accommodate this extra volume. Some cases of fluid in excess

of one liter within the pericardial cavity have been reported. Rapid accumulation of as little as 100 mL of fluid following trauma may trigger cardiac tamponade. Other common causes include myocardial rupture, pericarditis, cancer, or even cardiac surgery. Removal of this excess fluid requires insertion of drainage tubes into the pericardial cavity. Premature removal of these drainage tubes, for example, following cardiac surgery, or clot formation within these tubes are causes of this condition. Untreated, cardiac tamponade can lead to death.

External Anatomy of the Heart



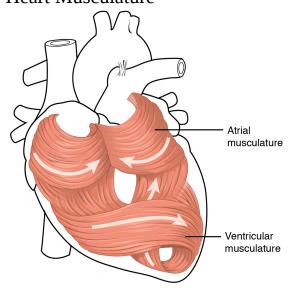
Inside the pericardium, the surface features of the heart are visible.

Layers

The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium (see [link]). The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.

The middle and thickest layer is the **myocardium**, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure 8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. [link] illustrates the arrangement of muscle cells.

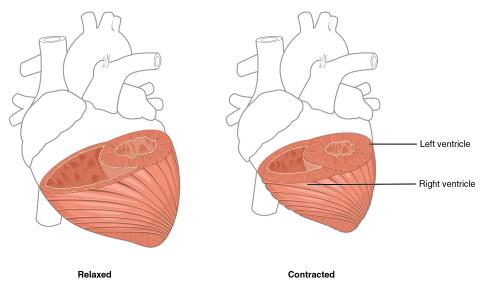
Heart Musculature



The swirling pattern of cardiac muscle tissue contributes significantly to the heart's ability to pump blood effectively.

Although the ventricles on the right and left sides pump the same volume of blood per contraction, the muscle of the left ventricle is much thicker and better developed than that of the right ventricle. In order to overcome the high resistance required to pump blood into the long systemic circuit, the left ventricle must generate a great amount of pressure. The right ventricle does not need to generate as much pressure, since the pulmonary circuit is shorter and provides less resistance. [link] illustrates the differences in muscular thickness needed for each of the ventricles.

Differences in Ventricular Muscle Thickness



The myometrium in the left ventricle is significantly thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed and contracting states. Note the differences in the relative size of the

lumens, the region inside each ventricle where the blood is contained.

The innermost layer of the heart wall, the **endocardium**, is joined to the myocardium with a thin layer of connective tissue. The endocardium lines the chambers where the blood circulates and covers the heart valves. It is made of simple squamous epithelium called **endothelium**, which is continuous with the endothelial lining of the blood vessels (see [link]).

Once regarded as a simple lining layer, recent evidence indicates that the endothelium of the endocardium and the coronary capillaries may play active roles in regulating the contraction of the muscle within the myocardium. The endothelium may also regulate the growth patterns of the cardiac muscle cells throughout life, and the endothelins it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

Internal Structure of the Heart

Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

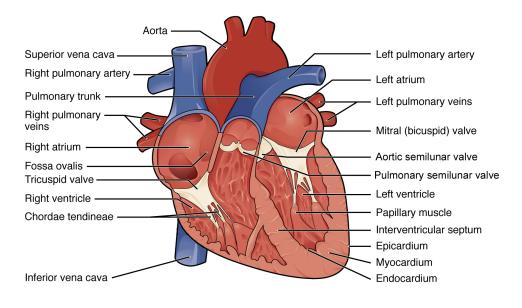
The word septum is derived from the Latin for "something that encloses;" in this case, a **septum** (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the

interatrial septum. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the fossa ovalis, a remnant of an opening in the fetal heart known as the foramen ovale. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the septum primum that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

Between the two ventricles is a second septum known as the **interventricular septum**. Unlike the interatrial septum, the interventricular septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the **atrioventricular septum.** It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a valve, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as **atrioventricular (AV) valves**. The valves at the openings that lead to the pulmonary trunk and aorta are known generically as **semilunar** (**SL**) **valves**. The interventricular septum is visible in [link]. In this figure, the atrioventricular septum has been removed to better show the bicupid and tricuspid valves; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the cardiac skeleton, or skeleton of the heart, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.

Internal Structures of the Heart



Anterior view

This anterior view of the heart shows the four chambers, the major vessels and their early branches, as well as the valves. The presence of the pulmonary trunk and aorta covers the interatrial septum, and the atrioventricular septum is cut away to show the

Note:

Disorders of the...

Heart: Heart Defects

One very common form of interatrial septum pathology is patent foramen ovale, which occurs when the septum primum does not close at birth, and the fossa ovalis is unable to fuse. The word patent is from the Latin root patens for "open." It may be benign or asymptomatic, perhaps never being diagnosed, or in extreme cases, it may require surgical repair to close the opening permanently. As much as 20–25 percent of the general population may have a patent foramen ovale, but fortunately, most have the benign, asymptomatic version. Patent foramen ovale is normally detected by

auscultation of a heart murmur (an abnormal heart sound) and confirmed by imaging with an echocardiogram. Despite its prevalence in the general population, the causes of patent ovale are unknown, and there are no known risk factors. In nonlife-threatening cases, it is better to monitor the condition than to risk heart surgery to repair and seal the opening. Coarctation of the aorta is a congenital abnormal narrowing of the aorta that is normally located at the insertion of the ligamentum arteriosum, the remnant of the fetal shunt called the ductus arteriosus. If severe, this condition drastically restricts blood flow through the primary systemic artery, which is life threatening. In some individuals, the condition may be fairly benign and not detected until later in life. Detectable symptoms in an infant include difficulty breathing, poor appetite, trouble feeding, or failure to thrive. In older individuals, symptoms include dizziness, fainting, shortness of breath, chest pain, fatigue, headache, and nosebleeds. Treatment involves surgery to resect (remove) the affected region or angioplasty to open the abnormally narrow passageway. Studies have shown that the earlier the surgery is performed, the better the chance of survival.

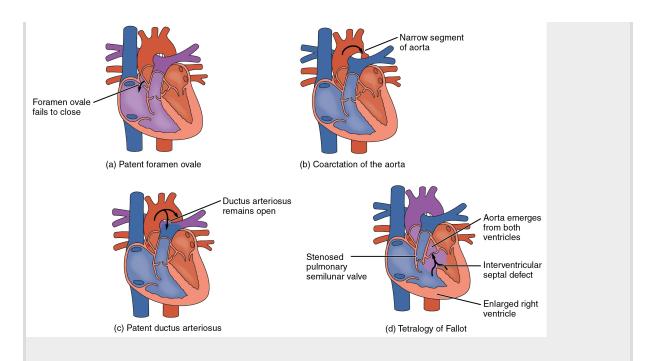
A patent ductus arteriosus is a congenital condition in which the ductus arteriosus fails to close. The condition may range from severe to benign. Failure of the ductus arteriosus to close results in blood flowing from the higher pressure aorta into the lower pressure pulmonary trunk. This additional fluid moving toward the lungs increases pulmonary pressure and makes respiration difficult. Symptoms include shortness of breath (dyspnea), tachycardia, enlarged heart, a widened pulse pressure, and poor weight gain in infants. Treatments include surgical closure (ligation), manual closure using platinum coils or specialized mesh inserted via the femoral artery or vein, or nonsteroidal anti-inflammatory drugs to block the synthesis of prostaglandin E2, which maintains the vessel in an open position. If untreated, the condition can result in congestive heart failure. Septal defects are not uncommon in individuals and may be congenital or caused by various disease processes. Tetralogy of Fallot is a congenital condition that may also occur from exposure to unknown environmental factors; it occurs when there is an opening in the interventricular septum caused by blockage of the pulmonary trunk, normally at the pulmonary semilunar valve. This allows blood that is relatively low in oxygen from the right ventricle to flow into the left ventricle and mix with the blood that

is relatively high in oxygen. Symptoms include a distinct heart murmur, low blood oxygen percent saturation, dyspnea or difficulty in breathing, polycythemia, broadening (clubbing) of the fingers and toes, and in children, difficulty in feeding or failure to grow and develop. It is the most common cause of cyanosis following birth. The term "tetralogy" is derived from the four components of the condition, although only three may be present in an individual patient: pulmonary infundibular stenosis (rigidity of the pulmonary valve), overriding aorta (the aorta is shifted above both ventricles), ventricular septal defect (opening), and right ventricular hypertrophy (enlargement of the right ventricle). Other heart defects may also accompany this condition, which is typically confirmed by echocardiography imaging. Tetralogy of Fallot occurs in approximately 400 out of one million live births. Normal treatment involves extensive surgical repair, including the use of stents to redirect blood flow and replacement of valves and patches to repair the septal defect, but the condition has a relatively high mortality. Survival rates are currently 75 percent during the first year of life; 60 percent by 4 years of age; 30 percent by 10 years; and 5 percent by 40 years.

In the case of severe septal defects, including both tetralogy of Fallot and patent foramen ovale, failure of the heart to develop properly can lead to a condition commonly known as a "blue baby." Regardless of normal skin pigmentation, individuals with this condition have an insufficient supply of oxygenated blood, which leads to cyanosis, a blue or purple coloration of the skin, especially when active.

Septal defects are commonly first detected through auscultation, listening to the chest using a stethoscope. In this case, instead of hearing normal heart sounds attributed to the flow of blood and closing of heart valves, unusual heart sounds may be detected. This is often followed by medical imaging to confirm or rule out a diagnosis. In many cases, treatment may not be needed. Some common congenital heart defects are illustrated in [link].

Congenital Heart Defects



(a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d) Tetralogy of Fallot includes an abnormal opening in the interventricular septum.

Right Atrium

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic circulation. The two major systemic veins, the superior and inferior venae cavae, and the large coronary vein called the **coronary sinus** that drains the heart myocardium empty into the right atrium. The superior vena cava drains blood from regions superior to the diaphragm: the head, neck, upper limbs, and the thoracic region. It empties into the right atrium. The inferior vena cava drains blood from areas inferior to the diaphragm: the lower limbs and abdominopelvic region of the body. It, too, empties into the right atrium. Immediately superior and slightly

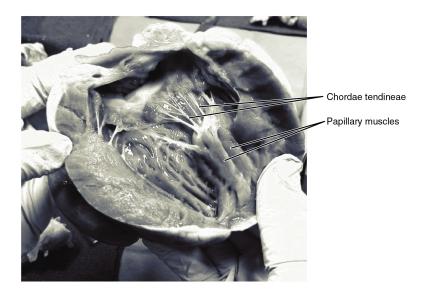
medial to the opening of the inferior vena cava on the posterior surface of the atrium is the opening of the coronary sinus. This thin-walled vessel drains most of the coronary veins that return systemic blood from the heart. The majority of the internal heart structures discussed in this and subsequent sections are illustrated in [link].

The atria receive venous blood on a nearly continuous basis, preventing venous flow from stopping while the ventricles are contracting. While most ventricular filling occurs while the atria are relaxed, they do demonstrate a contractile phase and actively pump blood into the ventricles just prior to ventricular contraction. The opening between the atrium and ventricle is guarded by the tricuspid valve.

Right Ventricle

The right ventricle receives blood from the right atrium through the tricuspid valve. Each flap of the valve is attached to strong strands of connective tissue, the **chordae tendineae**, literally "tendinous cords," or sometimes more poetically referred to as "heart strings." There are several chordae tendineae associated with each of the flaps. They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the flaps to a **papillary muscle** that extends from the inferior ventricular surface.

When the myocardium of the ventricle contracts, pressure within the ventricular chamber rises. Blood, like any fluid, flows from higher pressure to lower pressure areas, in this case, toward the pulmonary trunk and the atrium. To prevent any potential backflow, the papillary muscles also contract, generating tension on the chordae tendineae. This prevents the flaps of the valves from being forced into the atria and regurgitation of the blood back into the atria during ventricular contraction. [link] shows papillary muscles and chordae tendineae attached to the tricuspid valve. Chordae Tendineae and Papillary Muscles



In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae. (credit: modification of work by "PV KS"/flickr.com)

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

Left Atrium

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the

left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the both atria will contract, pumping blood into the ventricles. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve, which is also called the bicuspid valve.

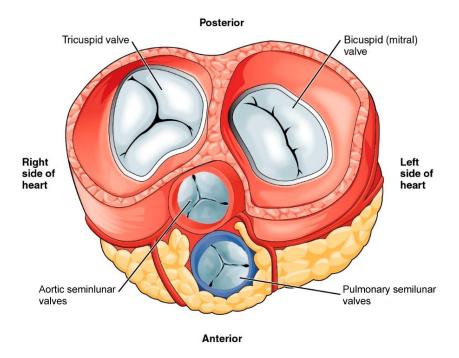
Left Ventricle

Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right (see [link]). The mitral valve is connected to papillary muscles via chordae tendineae. The purpose of the chordae tendinae in the left ventricle is the same as in the right ventricle.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

Heart Valve Structure and Function

A transverse section through the heart slightly above the level of the atrioventricular septum reveals all four heart valves along the same plane ([link]). The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the **right atrioventricular valve**, or **tricuspid valve**. It typically consists of three flaps, or leaflets, made of endocardium reinforced with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves. Heart Valves



With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or the **pulmonary SL valve**; it is also known as the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes, the pressure differential causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close. The turbulent blood flow as the valve closes producs an audible sound. Unlike the atrioventricular valves, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

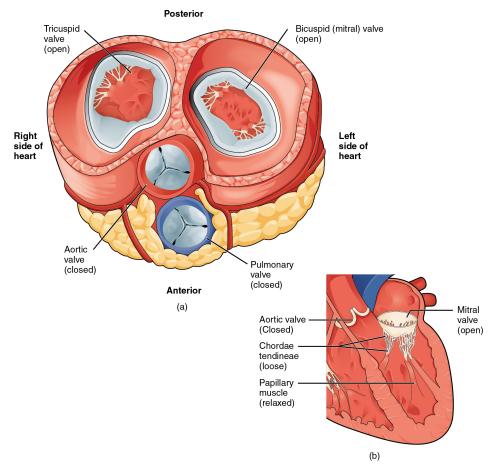
Located at the opening between the left atrium and left ventricle is the **mitral valve**, also called the **bicuspid valve** or the **left atrioventricular valve**. Structurally, this valve consists of two cusps. In a clinical setting, the valve is referred to as the mitral valve, rather than the bicuspid valve. The

two cusps of the mitral valve are attached by chordae tendineae to two papillary muscles that project from the wall of the ventricle.

At the base of the aorta is the aortic semilunar valve, or the **aortic SL valve**, which prevents backflow from the aorta. It normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

In [link]a, the two atrioventricular valves are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and when the atria contract to pump blood into the ventricles. [link]b shows a frontal view. Although only the left side of the heart is illustrated, the process is virtually identical on the right.

Blood Flow from the Left Atrium to the Left Ventricle

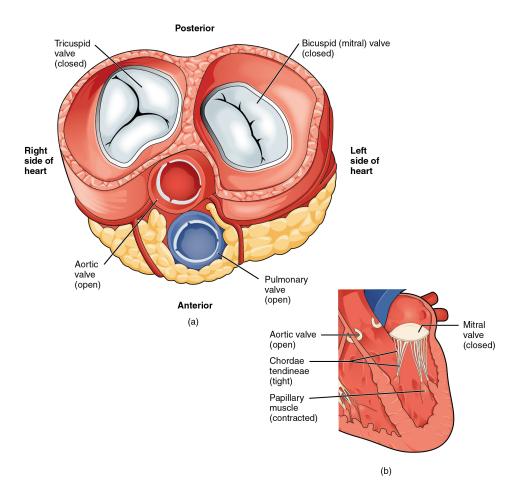


(a) A transverse section through the heart illustrates

the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the mitral valve is open, it allows blood to move from the left atrium to the left ventricle. The aortic semilunar valve is closed to prevent backflow of blood from the aorta to the left ventricle.

[link]a shows the atrioventricular valves closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two atrioventricular valves prevents blood from being forced back into the atria. This stage can be seen from a frontal view in [link]b.

Blood Flow from the Left Ventricle into the Great Vessels



(a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.

When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the

papillary muscles are also relaxed and the tension on the chordae tendineae is slight (see [link]b). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (see [link]b), helping to hold the cusps of the atrioventricular valves in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the atrioventricular valves. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

Note:



Visit this <u>site</u> to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been "removed" from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Note:

Disorders of the...

Heart Valves

When heart valves do not function properly, they are often described as incompetent and result in valvular heart disease, which can range from benign to lethal. Some of these conditions are congenital, that is, the individual was born with the defect, whereas others may be attributed to

disease processes or trauma. Some malfunctions are treated with medications, others require surgery, and still others may be mild enough that the condition is merely monitored since treatment might trigger more serious consequences.

Valvular disorders are often caused by carditis, or inflammation of the heart. One common trigger for this inflammation is rheumatic fever, or scarlet fever, an autoimmune response to the presence of a bacterium, *Streptococcus pyogenes*, normally a disease of childhood.

While any of the heart valves may be involved in valve disorders, mitral regurgitation is the most common, detected in approximately 2 percent of the population, and the pulmonary semilunar valve is the least frequently involved. When a valve malfunctions, the flow of blood to a region will often be disrupted. The resulting inadequate flow of blood to this region will be described in general terms as an insufficiency. The specific type of insufficiency is named for the valve involved: aortic insufficiency, mitral insufficiency, tricuspid insufficiency, or pulmonary insufficiency.

If one of the cusps of the valve is forced backward by the force of the blood, the condition is referred to as a prolapsed valve. Prolapse may occur if the chordae tendineae are damaged or broken, causing the closure mechanism to fail. The failure of the valve to close properly disrupts the normal one-way flow of blood and results in regurgitation, when the blood flows backward from its normal path. Using a stethoscope, the disruption to the normal flow of blood produces a heart murmur.

Stenosis is a condition in which the heart valves become rigid and may calcify over time. The loss of flexibility of the valve interferes with normal function and may cause the heart to work harder to propel blood through the valve, which eventually weakens the heart. Aortic stenosis affects approximately 2 percent of the population over 65 years of age, and the percentage increases to approximately 4 percent in individuals over 85 years. Occasionally, one or more of the chordae tendineae will tear or the papillary muscle itself may die as a component of a myocardial infarction (heart attack). In this case, the patient's condition will deteriorate dramatically and rapidly, and immediate surgical intervention may be required.

Auscultation, or listening to a patient's heart sounds, is one of the most useful diagnostic tools, since it is proven, safe, and inexpensive. The term auscultation is derived from the Latin for "to listen," and the technique has

been used for diagnostic purposes as far back as the ancient Egyptians. Valve and septal disorders will trigger abnormal heart sounds. If a valvular disorder is detected or suspected, a test called an echocardiogram, or simply an "echo," may be ordered. Echocardiograms are sonograms of the heart and can help in the diagnosis of valve disorders as well as a wide variety of heart pathologies.

Note:



Visit this <u>site</u> for a free download, including excellent animations and audio of heart sounds.

Note:

Career Connection

Cardiologist

Cardiologists are medical doctors that specialize in the diagnosis and treatment of diseases of the heart. After completing 4 years of medical school, cardiologists complete a three-year residency in internal medicine followed by an additional three or more years in cardiology. Following this 10-year period of medical training and clinical experience, they qualify for a rigorous two-day examination administered by the Board of Internal Medicine that tests their academic training and clinical abilities, including diagnostics and treatment. After successful completion of this examination, a physician becomes a board-certified cardiologist. Some board-certified cardiologists may be invited to become a Fellow of the American College of Cardiology (FACC). This professional recognition is awarded to outstanding physicians based upon merit, including outstanding

credentials, achievements, and community contributions to cardiovascular medicine.

Note:



Visit this <u>site</u> to learn more about cardiologists.

Note:

Career Connection

Cardiovascular Technologist/Technician

Cardiovascular technologists/technicians are trained professionals who perform a variety of imaging techniques, such as sonograms or echocardiograms, used by physicians to diagnose and treat diseases of the heart. Nearly all of these positions require an associate degree, and these technicians earn a median salary of \$49,410 as of May 2010, according to the U.S. Bureau of Labor Statistics. Growth within the field is fast, projected at 29 percent from 2010 to 2020.

There is a considerable overlap and complementary skills between cardiac technicians and vascular technicians, and so the term cardiovascular technician is often used. Special certifications within the field require documenting appropriate experience and completing additional and often expensive certification examinations. These subspecialties include Certified Rhythm Analysis Technician (CRAT), Certified Cardiographic Technician (CCT), Registered Congenital Cardiac Sonographer (RCCS), Registered Cardiac Electrophysiology Specialist (RCES), Registered Cardiovascular Invasive Specialist (RCIS), Registered Cardiac

Sonographer (RCS), Registered Vascular Specialist (RVS), and Registered Phlebology Sonographer (RPhS).

Note:



Visit this <u>site</u> for more information on cardiovascular technologists/technicians.

Coronary Circulation

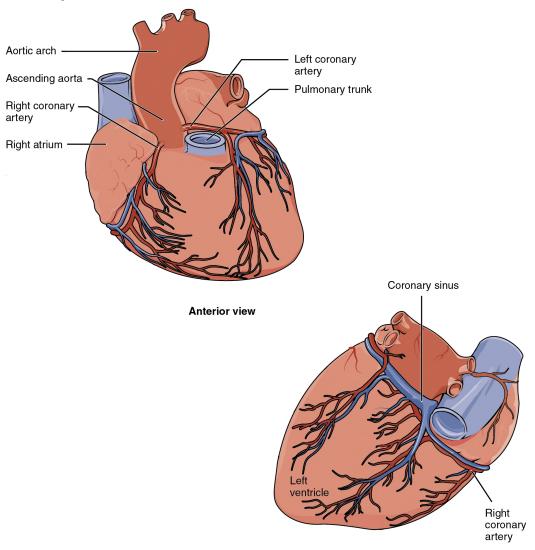
You will recall that the heart is a remarkable pump composed largely of cardiac muscle cells that are incredibly active throughout life. Like all other cells, a **cardiomyocyte** requires a reliable supply of oxygen and nutrients, and a way to remove wastes, so it needs a dedicated, complex, and extensive coronary circulation. And because of the critical and nearly ceaseless activity of the heart throughout life, this need for a blood supply is even greater than for a typical cell. However, coronary circulation is not continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

Coronary Arteries

Coronary arteries supply blood to the myocardium and other components of the heart. The first portion of the aorta after it arises from the left ventricle gives rise to the coronary arteries. The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle,

and the interventricular septum. The right coronary artery distributes blood to the right atrium, portions of both ventricles, and the heart conduction system [link].

Coronary Circulation



Posterior view

The anterior view of the heart shows the prominent coronary surface vessels. The posterior view of the heart shows the prominent coronary surface vessels.

Note:

Diseases of the...

Heart: Myocardial Infarction

Myocardial infarction (MI) is the formal term for what is commonly referred to as a heart attack. It normally results from a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart, resulting in death of the cardiac muscle cells. An MI often occurs when a coronary artery is blocked by the buildup of atherosclerotic plaque consisting of lipids, cholesterol and fatty acids, and white blood cells, primarily macrophages. It can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels. The resulting blockage restricts the flow of blood and oxygen to the myocardium and causes death of the tissue. MIs may be triggered by excessive exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel. In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms.

An MI can be confirmed by examining the patient's ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells.

Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future.

MIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as "bad" cholesterol), low levels of high-density lipoprotein (HDL, or "good" cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

Coronary Veins

Coronary veins drain the heart and generally parallel the large surface arteries (see [link]). The coronary veins deliver blood to the coronary sinus which will drain directly into the right atrium.

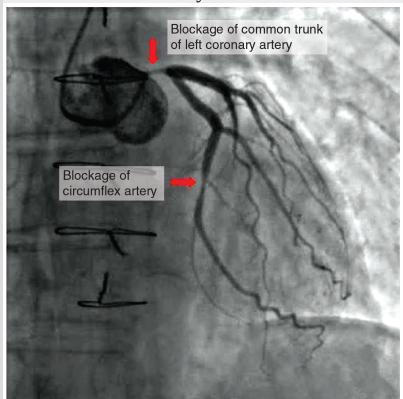
Note:

Diseases of the...

Heart: Coronary Artery Disease

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque—a fatty material including cholesterol, connective tissue, white blood cells, and some smooth muscle cells—within the walls of the arteries obstructs the flow of blood and decreases the flexibility or compliance of the vessels. This condition is called atherosclerosis, a hardening of the arteries that involves the accumulation of plaque. As the coronary blood vessels become occluded, the flow of blood to the tissues will be restricted, a condition called ischemia that causes the cells to receive insufficient amounts of oxygen, called hypoxia. [link] shows the blockage of coronary arteries highlighted by the injection of dye. Some individuals with coronary artery disease report pain radiating from the chest called angina pectoris, but others remain asymptomatic. If untreated, coronary artery disease can lead to MI or a heart attack.

Atherosclerotic Coronary Arteries



In this coronary angiogram (X-ray), the dye makes visible two occluded coronary arteries. Such blockages can lead to decreased blood flow (ischemia) and insufficient oxygen (hypoxia) delivered to the cardiac tissues. If uncorrected, this can lead to cardiac muscle death (myocardial infarction).

The disease progresses slowly and often begins in children and can be seen as fatty "streaks" in the vessels. It then gradually progresses throughout life. Well-documented risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia or high circulating levels of lipids in the blood. Treatments may include medication, changes to diet and exercise, angioplasty with a balloon catheter, insertion of a stent, or coronary bypass procedure.

Angioplasty is a procedure in which the occlusion is mechanically widened with a balloon. A specialized catheter with an expandable tip is inserted into a superficial vessel, normally in the leg, and then directed to the site of the occlusion. At this point, the balloon is inflated to compress the plaque material and to open the vessel to increase blood flow. Then, the balloon is deflated and retracted. A stent consisting of a specialized mesh is typically inserted at the site of occlusion to reinforce the weakened and damaged walls. Stent insertions have been routine in cardiology for more than 40 years.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

Chapter Review

The heart resides within the pericardial sac and is located in the mediastinal space within the thoracic cavity. The pericardial sac consists of two fused layers: an outer fibrous capsule and an inner parietal pericardium lined with a serous membrane. Between the pericardial sac and the heart is the pericardial cavity, which is filled with lubricating serous fluid. The walls of the heart are composed of an outer epicardium, a thick myocardium, and an inner lining layer of endocardium. The human heart consists of a pair of atria, which receive blood and pump it into a pair of ventricles, which pump blood into the vessels. The right atrium receives systemic blood relatively low in oxygen and pumps it into the right ventricle, which pumps it into the pulmonary circuit. Exchange of oxygen and carbon dioxide occurs in the lungs, and blood high in oxygen returns to the left atrium, which pumps blood into the left ventricle, which in turn pumps blood into the aorta and the remainder of the systemic circuit. The septa are the partitions that separate the chambers of the heart. They include the interatrial septum, the interventricular septum, and the atrioventricular septum. Two of these openings are guarded by the atrioventricular valves, the right tricuspid valve and the left mitral valve, which prevent the backflow of blood. Each is attached to chordae tendineae that extend to the papillary muscles, which are extensions of the myocardium, to prevent the valves from being blown back into the atria. The pulmonary valve is located at the base of the pulmonary trunk, and the left semilunar valve is located at the base of the aorta. The right and left coronary arteries are the first to branch off the aorta and arise from two of the three sinuses located near the base of the aorta and are generally located in the sulci. Cardiac veins parallel the small cardiac arteries and generally drain into the coronary sinus.

Glossary

aortic valve

(also, aortic semilunar valve) valve located at the base of the aorta

atrioventricular septum

cardiac septum located between the atria and ventricles; atrioventricular valves are located here

atrioventricular (AV) valves

one-way valves located between the atria and ventricles; the valve on the right is called the tricuspid valve, and the one on the left is the mitral or bicuspid valve

atrium

(plural = atria) upper or receiving chamber of the heart that pumps blood into the lower chambers just prior to their contraction; the right atrium receives blood from the systemic circuit that flows into the right ventricle; the left atrium receives blood from the pulmonary circuit that flows into the left ventricle

bicuspid valve

(also, mitral valve or left atrioventricular valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

cardiac notch

depression in the medial surface of the inferior lobe of the left lung where the apex of the heart is located

cardiomyocyte

muscle cell of the heart

chordae tendineae

string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

coronary arteries

branches of the ascending aorta that supply blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

coronary sinus

large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium

coronary veins

vessels that drain the heart and generally parallel the large surface arteries

endocardium

innermost layer of the heart lining the heart chambers and heart valves; composed of endothelium reinforced with a thin layer of connective tissue that binds to the myocardium

endothelium

layer of smooth, simple squamous epithelium that lines the endocardium and blood vessels

epicardium

innermost layer of the serous pericardium and the outermost layer of the heart wall

hypertrophic cardiomyopathy

pathological enlargement of the heart, generally for no known reason

inferior vena cava

large systemic vein that returns blood to the heart from the inferior portion of the body

interatrial septum

cardiac septum located between the two atria; contains the fossa ovalis after birth

interventricular septum

cardiac septum located between the two ventricles

left atrioventricular (AV) valve

(also, mitral valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

mesothelium

simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the

deepest portion of the pericardium (the parietal pericardium)

mitral valve

(also, left atrioventricular valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

myocardium

thickest layer of the heart composed of cardiac muscle cells built upon a framework of primarily collagenous fibers and blood vessels that supply it and the nervous fibers that help to regulate it

papillary muscle

extension of the myocardium in the ventricles to which the chordae tendineae attach

pericardial cavity

cavity surrounding the heart filled with a lubricating serous fluid that reduces friction as the heart contracts

pericardial sac

(also, pericardium) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

pericardium

(also, pericardial sac) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

pulmonary arteries

left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs

pulmonary capillaries

capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters

pulmonary circuit

blood flow to and from the lungs

pulmonary semilunar valve

(also, pulmonary valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps

pulmonary trunk

large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

pulmonary veins

veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

right atrioventricular valve

(also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of tissue

semilunar (SL) valves

valves located at the base of the pulmonary trunk and at the base of the aorta

septum

(plural = septa) walls or partitions that divide the heart into chambers

superior vena cava

large systemic vein that returns blood to the heart from the superior portion of the body

systemic circuit

blood flow to and from virtually all of the tissues of the body

tricuspid valve

term used most often in clinical settings for the right atrioventricular valve

valve

in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

ventricle

one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium

OU Human Physiology: Cardiac Muscle and Electrical Activity By the end of this section, you will be able to:

- Describe the structure of cardiac muscle
- Identify and describe the role of each component in the cardiac conduction system
- Relate the cardiac conduction system to the mechanical work of the cardiac contractile cells
- Compare and contrast the cells, channels, and ion movement involved in generating pacemaker potentials, pacemaker action potentials, and a cardiac action potentials
- Explain the importance of an extended absolute refractory period in cardiac action potentials
- Discuss the electrical events occurring during the waves and segments in an ECG
- Relate the electrical events of an ECG to the mechanical events in the heart including events in the cardiac cycle
- Differentiate between normal and abnormal ECGs
- Identify blocks that can interrupt the cardiac cycle

Recall that cardiac muscle shares a few characteristics with both skeletal muscle and smooth muscle, but it has some unique properties of its own. Not the least of these exceptional properties is its ability to initiate an electrical potential at a fixed rate that spreads rapidly from cell to cell to trigger the contractile mechanism. This property is known as **autorhythmicity**. Neither smooth nor skeletal muscle can do this. Even though cardiac muscle has autorhythmicity, heart rate is modulated by the endocrine and nervous systems.

There are two major types of cardiac muscle cells: cardiac contractile cells (myocardial contractile cells or myocytes) and autorhythmic or pacemaker cells (myocardial conducting cells). The **cardiac contractile cells** constitute the bulk (99 percent) of the cells in the atria and ventricles. Contractile cells conduct impulses and are responsible for contractions that pump blood through the body. In other words, these cells do the mechanical work; they contract which generates the force to pump the blood. These cells create cardiac potentials. A topic that we will return to later. The **autorhythmic**

cells or pacemaker cells (1 percent of the cells) form the conduction system of the heart. Except for Purkinje cells, they are generally much smaller than the cardiac contractile cells and have few of the myofibrils or filaments needed for contraction. Their function is similar in many respects to neurons, although they are specialized muscle cells. Autorhythmic cells initiate and propagate the action potential (the electrical impulse) that travels throughout the heart setting the heart rate and triggers the cardiac contractile cells to contract and therefore propel the blood. These autorhythmic cells create pacemaker potentials. Another topic that we will return to later.

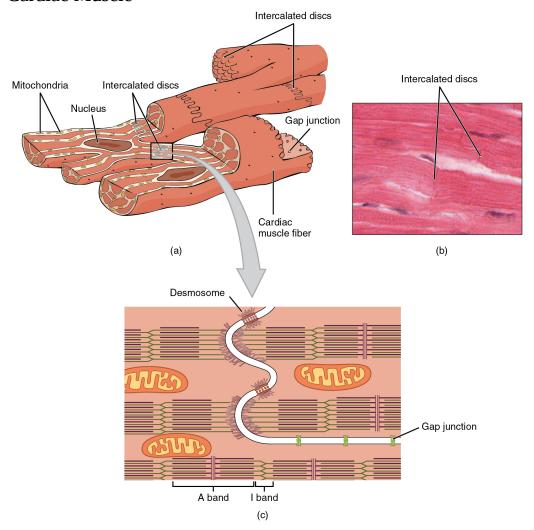
Structure of Cardiac Muscle

Compared to the giant cylinders of skeletal muscle, cardiac muscle cells, or cardiomyocytes, are considerably shorter with much smaller diameters. Cardiac muscle also demonstrates striations, the alternating pattern of dark A bands and light I bands attributed to the precise arrangement of the myofilaments and fibrils that are organized in sarcomeres along the length of the cell ([link]a). These contractile elements are virtually identical to skeletal muscle. T (transverse) tubules penetrate from the surface plasma membrane, the sarcolemma, to the interior of the cell, allowing the electrical impulse to reach the interior. The T tubules are only found at the Z discs, whereas in skeletal muscle, they are found at the junction of the A and I bands. Therefore, there are one-half as many T tubules in cardiac muscle as in skeletal muscle. In addition, the sarcoplasmic reticulum stores few calcium ions, so most of the calcium ions must come from outside the cells. The result is a slower onset of contraction. Mitochondria are plentiful, providing energy for the contractions of the heart. Typically, cardiomyocytes have a single, central nucleus, but two or more nuclei may be found in some cells.

Cardiac muscle cells branch freely. A junction between two adjoining cells is marked by a critical structure called an **intercalated disc**, which helps support the synchronized contraction of the muscle ([link]b). The sarcolemmas from adjacent cells bind together at the intercalated discs. They consist of desmosomes, specialized linking proteoglycans, tight junctions, and large numbers of gap junctions that allow the passage of ions

between the cells and help to synchronize the contraction ([link]c). Intercellular connective tissue also helps to bind the cells together. The importance of strongly binding these cells together is necessitated by the forces exerted by contraction.

Cardiac Muscle



(a) Cardiac muscle cells have myofibrils composed of myofilaments arranged in sarcomeres, T tubules to transmit the impulse from the sarcolemma to the interior of the cell, numerous mitochondria for energy, and intercalated discs that are found at the junction of different cardiac muscle cells. (b) A photomicrograph of cardiac muscle cells shows the nuclei and intercalated discs. (c) An intercalated disc connects cardiac muscle cells and consists of desmosomes

and gap junctions. LM × 1600. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Cardiac muscle undergoes aerobic respiration patterns, primarily metabolizing lipids and carbohydrates. Myoglobin, lipids, and glycogen are all stored within the cytoplasm. Cardiac muscle cells undergo twitch-type contractions with long refractory periods followed by brief relaxation periods. The relaxation is essential so the heart can fill with blood for the next cycle. The refractory period is very long to prevent the possibility of tetanus, a condition in which muscle remains involuntarily contracted. In the heart, tetanus is not compatible with life, since it would prevent the heart from pumping blood.

Note:

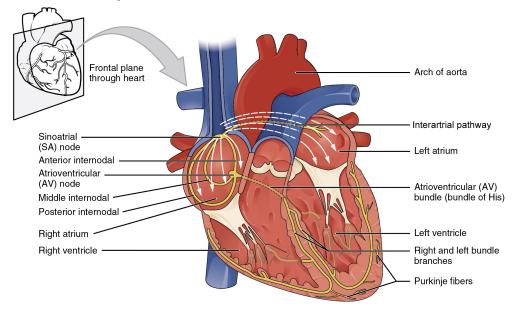
Everyday Connection Repair and Replacement

Damaged cardiac muscle cells have extremely limited abilities to repair themselves or to replace dead cells via mitosis. Recent evidence indicates that at least some stem cells remain within the heart that continue to divide and at least potentially replace these dead cells. However, newly formed or repaired cells are rarely as functional as the original cells, and cardiac function is reduced. In the event of a heart attack or MI, dead cells are often replaced by patches of scar tissue. Autopsies performed on individuals who had successfully received heart transplants show some proliferation of original cells. If researchers can unlock the mechanism that generates new cells and restore full mitotic capabilities to heart muscle, the prognosis for heart attack survivors will be greatly enhanced. To date, myocardial cells produced within the patient (*in situ*) by cardiac stem cells seem to be nonfunctional, although those grown in Petri dishes (*in vitro*) do beat. Perhaps soon this mystery will be solved, and new advances in treatment will be commonplace.

Conduction System of the Heart

If embryonic heart cells are separated into a Petri dish and kept alive, each is capable of generating its own electrical impulse followed by contraction. When two independently beating embryonic cardiac muscle cells are placed together, the cell with the higher inherent rate sets the pace, and the impulse spreads from the faster to the slower cell to trigger a contraction. As more cells are joined together, the fastest cell continues to assume control of the rate. A fully developed adult heart maintains the capability of generating its own electrical impulse, triggered by the fastest cells, as part of the cardiac conduction system. The components of the cardiac conduction system include the sinoatrial node, the atrioventricular node, the atrioventricular bundle, the atrioventricular bundle branches, and the Purkinje cells ([link]).

Conduction System of the Heart



Anterior view of frontal section

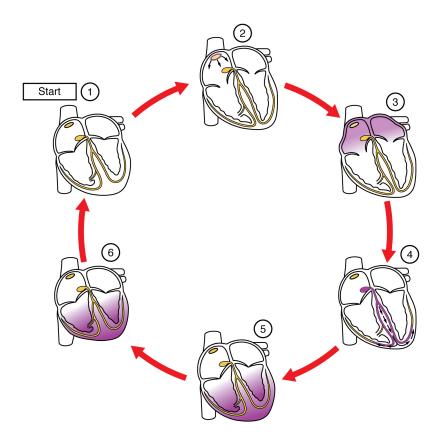
Specialized conducting components of the heart include the sinoatrial node, the internodal pathways, the atrioventricular node, the atrioventricular bundle, the right and left bundle branches, and the Purkinje fibers.

Sinoatrial (SA) Node

Normal cardiac rhythm is established by the **sinoatrial (SA) node**, a specialized clump of autorhythmic cells located in the superior and posterior walls of the right atrium in close proximity to the orifice of the superior vena cava. The SA node has the highest inherent rate of depolarization and is known as the **pacemaker** of the heart. It initiates the **sinus rhythm**, or normal electrical pattern followed by contraction of the heart.

This impulse spreads from its initiation in the SA node throughout the atria through specialized **internodal pathways**, to the atrial myocardial contractile cells and the atrioventricular node (see [link]). The impulse takes approximately 50 ms (milliseconds) to travel between these two nodes. The relative importance of this pathway has been debated since the impulse would reach the atrioventricular node simply following the cell-by-cell pathway through the contractile cells of the myocardium in the atria. In addition, there is a specialized pathway called the **interatrial pathway** (Bachmann's bundle) that conducts the impulse directly from the right atrium to the left atrium. Regardless of the pathway, as the impulse reaches the atrioventricular septum, the connective tissue of the cardiac skeleton prevents the impulse from spreading into the myocardial cells in the ventricles except at the atrioventricular node. [link] illustrates the initiation of the impulse in the SA node that then spreads the impulse throughout the atria to the atrioventricular node.

Cardiac Conduction



(1) The sinoatrial (SA) node and the remainder of the conduction system are at rest. (2) The SA node initiates the action potential, which sweeps across the atria. (3) After reaching the atrioventricular node, there is a delay of approximately 100 ms that allows the atria to complete pumping blood before the impulse is transmitted to the atrioventricular bundle. (4) Following the delay, the impulse travels through the atrioventricular bundle and bundle branches to the Purkinje fibers, and also reaches the right papillary muscle. (5) The impulse spreads to the contractile fibers of the ventricle. (6) Ventricular contraction begins.

The electrical event, the wave of depolarization, is the trigger for muscular contraction. The wave of depolarization begins in the right atrium, and the impulse spreads across both atria and then down through the contractile cells. The contractile cells then begin contraction from the base to the apex of the atria, efficiently pumping blood into the ventricles.

Atrioventricular (AV) Node

The **atrioventricular (AV) node** is a second clump of specialized autorhythmic cells, located in the inferior portion of the right atrium within the atrioventricular septum. The septum prevents the impulse from spreading directly to the ventricles without passing through the AV node. There is a critical pause before the AV node depolarizes and transmits the impulse to the atrioventricular bundle (see [link], step 3). This delay in transmission is partially attributable to the small diameter of the cells of the node, which slow the impulse. Also, conduction between nodal cells is less efficient than between conducting cells. These factors mean that it takes the impulse approximately 100 ms to pass through the node. This pause is critical to heart function, as it allows the atrial cardiomyocytes to complete their contraction that pumps blood into the ventricles before the impulse is transmitted to the cells of the ventricle itself. With extreme stimulation by the SA node, the AV node can transmit impulses maximally at 220 per minute. This establishes the typical maximum heart rate in a healthy young individual. Damaged hearts or those stimulated by drugs can contract at higher rates, but at these rates, the heart can no longer effectively pump blood.

Atrioventricular Bundle (Bundle of His), Bundle Branches, and Purkinje Fibers

Arising from the AV node, the **atrioventricular bundle**, or **bundle of His**, proceeds through the interventricular septum before dividing into two **atrioventricular bundle branches**, commonly called the left and right bundle branches. The left bundle branch supplies the left ventricle, and the

right bundle branch the right ventricle. Since the left ventricle is much larger than the right, the left bundle branch is also considerably larger than the right. Portions of the right bundle branch supply the right papillary muscles. Because of this connection, each papillary muscle receives the impulse at approximately the same time, so they begin to contract simultaneously just prior to the remainder of the myocardial contractile cells of the ventricles. This is believed to allow tension to develop on the chordae tendineae prior to right ventricular contraction. Both bundle branches descend and reach the apex of the heart where they connect with the Purkinje fibers (see [link], step 4). This passage takes approximately 25 ms.

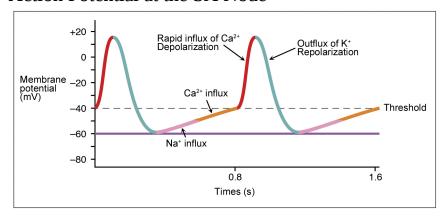
The **Purkinje fibers** are additional autorhythmic fibers that spread the impulse to the cardiac contractile cells in the ventricles. They extend throughout the myocardium from the apex of the heart toward the atrioventricular septum and the base of the heart. The Purkinje fibers have a fast inherent conduction rate, and the electrical impulse reaches all of the ventricular muscle cells in about 75 ms (see [link], step 5). Since the electrical stimulus begins at the apex, the contraction also begins at the apex and travels toward the base of the heart, similar to squeezing a tube of toothpaste from the bottom. This allows the blood to be pumped out of the ventricles and into the aorta and pulmonary trunk. The total time elapsed from the initiation of the impulse in the SA node until depolarization of the ventricles is approximately 225 ms.

Membrane Potentials and Ion Movement in Autorhythmic Cells

Action potentials are considerably different between autorhythmic cells and cardiac contractile cells. Cardiac contractile cells produce cardiac action potentials while autorhymthic cells produce pacemaker potentials and pacemaker action potentials. Here we will focus on the autorhymthic cells, the pacemaker potential and pacemaker action potential. Unlike skeletal muscles and neurons, autorhythmic cells do not have a stable resting potential. Autorhythmic cells contain a series of sodium ion channels that open and close. When open, Na⁺ influx occurs causing a change in the membrane potential which causes voltage-gated T-type Ca²⁺ channels to

open and Na $^+$ to close. "T" stands for transient as these channels stay open for a short period of time. When open, Ca $^{2+}$ influx will occur. The resulting depolarization from -60 mV to -40 mV is called a pacemaker potential. At threshold (-40 mV), the voltage-gated T-type Ca $^{2+}$ channels are closed and the voltage-gated L-type Ca $^{2+}$ channels open. "L" stands for long lasting as these channels remain open for a longer period of time. When open, Ca $^{2+}$ enters the cell, further depolarizing the cell at a more rapid rate until it reaches a value of approximately +5 mV. At this point, the calcium ion channels close and voltage-gated K $^+$ channels open, allowing efflux of K $^+$ and resulting in repolarization. When the membrane potential reaches approximately $^-$ 60 mV, the K $^+$ channels close and Na $^+$ channels open, and the pacemaker potential phase begins again. This phenomenon explains the autorhythmicity properties of autorhythmic cells in cardiac muscle ([link]).

Action Potential at the SA Node



The pacemaker potential (slow depolarization) is due to an influx of sodium ions which causes voltage-gated T-type calcium channels to open.

The influx of sodium and then calcium depolarizes the cell from -60 mV to -40 mV. At -40 mV, L-type calcium channels open causing further depolarization. When the membrane potential reaches +5 mV the L-type calcium channels close and voltage-gated potassium channels open. The efflux of potassium results in repolarization of the membrane to -60 mV. At -60 mV the potassium channels close and the sodium channels open. The pacemaker potential

accounts for the membrane reaching threshold and initiates the spontaneous depolarization and contraction of the cell. Note the lack of a stable resting membrane potential.

Membrane Potentials and Ion Movement in Cardiac Contractile Cells

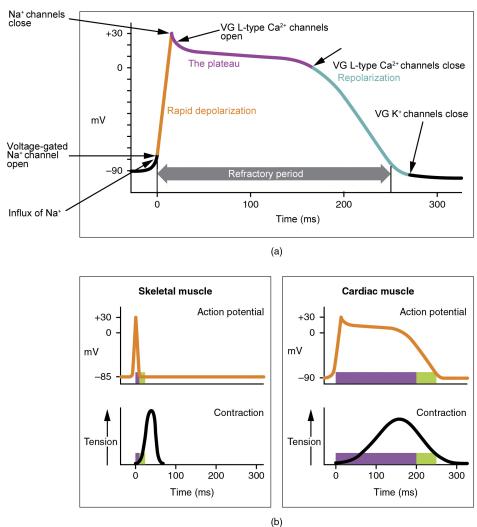
There is a distinctly different electrical pattern involving the contractile cells. In this case, there is a rapid depolarization, followed by a brief repolarization phase, a plateau, and then repolarization. This phenomenon accounts for the long refractory periods required for the cardiac muscle cells to pump blood effectively before they are capable of firing for a second time. These cardiac myocytes normally do not initiate their own electrical potential, although they are capable of doing so, but rather wait for an impulse to reach them.

Contractile cells demonstrate a much more stable resting phase than conductive cells at approximately –80 mV for cells in the atria and –90 mV for cells in the ventricles. Despite this initial difference, the other components of their action potentials are virtually identical. In both cases, when stimulated by an action potential via adjacent autorhythmic cells or cardiac contractile cells, voltage-gated Na⁺ channels rapidly open, beginning the positive-feedback mechanism of depolarization. This rapid influx of positive sodium ions raises the membrane potential to approximately +30 mV, at which point the sodium channels close. The rapid depolarization period typically lasts 3–5 ms. Depolarization is followed by a brief repolarization and a plateau phase, in which the membrane potential declines relatively slowly. This is due in large part to the opening of the voltage-gated L-type Ca²⁺ channels, allowing Ca²⁺ to enter the cell while few K⁺ channels are open, allowing K⁺ to exit the cell. The relatively long plateau phase lasts approximately 175 ms. Once the membrane potential reaches approximately zero, the Ca²⁺ channels close and voltage-gated K⁺ channels open, allowing K⁺ to exit the cell. The repolarization lasts approximately 75 ms. At this point, membrane potential drops until it

reaches resting levels once more and the cycle repeats. The entire event lasts between 250 and 300 ms ([link]).

The absolute refractory period for cardiac contractile muscle lasts approximately 200 ms. This extended period is critical, since the heart muscle must contract to pump blood effectively and the contraction must follow the electrical events. Without extended refractory periods, premature contractions would occur in the heart and would not be compatible with life.

Action Potential in Cardiac Contractile Cells



(a) Note the long plateau phase due to the influx of calcium ions. The extended refractory period allows the cell to fully contract before another electrical event

can occur. (b) The action potential for heart muscle is compared to that of skeletal muscle.

Calcium Ions

Calcium ions play two critical roles in the physiology of cardiac muscle. Their influx through slow calcium channels accounts for the prolonged plateau phase and absolute refractory period that enable cardiac muscle to function properly. Calcium ions also combine with the regulatory protein troponin in the troponin-tropomyosin complex; this complex removes the inhibition that prevents the heads of the myosin molecules from forming cross bridges with the active sites on actin that provide the power stroke of contraction. This mechanism is virtually identical to that of skeletal muscle. Approximately 20 percent of the calcium required for contraction is supplied by the influx of Ca²⁺ during the plateau phase. The remaining Ca²⁺ for contraction is released from storage in the sarcoplasmic reticulum.

Comparative Rates of Conduction System Firing

The pattern of spontaneous slow depolarization, followed by rapid depolarization and repolarization just described in the pacemaker action potential, are seen in the SA node and a few other conductive cells in the heart. Since the SA node is the pacemaker, it reaches threshold faster than any other component of the conduction system. It will initiate the impulses spreading to the other conducting cells. The SA node, without nervous or endocrine control, would initiate a heart impulse approximately 80–100 times per minute. Although each component of the conduction system is capable of generating its own impulse, the rate progressively slows as you proceed from the SA node to the Purkinje fibers. Without the SA node, the AV node would generate a heart rate of 40–60 beats per minute. If the AV node were blocked, the atrioventricular bundle would fire at a rate of approximately 30–40 impulses per minute. The bundle branches would

have an inherent rate of 20–30 impulses per minute, and the Purkinje fibers would fire at 15–20 impulses per minute. While a few exceptionally trained aerobic athletes demonstrate resting heart rates in the range of 30–40 beats per minute (the lowest recorded figure is 28 beats per minute for Miguel Indurain, a cyclist), for most individuals, rates lower than 50 beats per minute would indicate a condition called bradycardia. Depending upon the specific individual, as rates fall much below this level, the heart would be unable to maintain adequate flow of blood to vital tissues, initially resulting in decreasing loss of function across the systems, unconsciousness, and ultimately death ([link]).

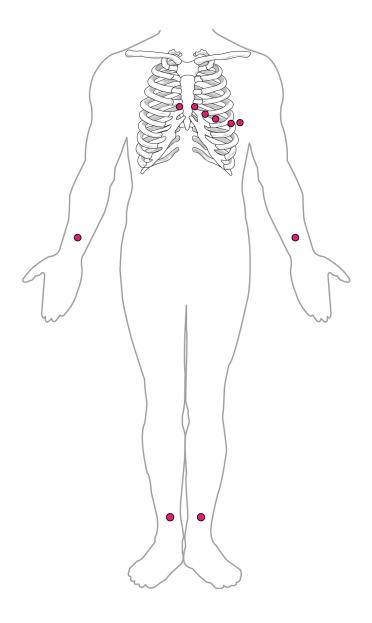
Conduction fiber	Action potentials per minute	Location	Comments
SA node	80-100	Top of right atrium	Sets the HR
AV node	40-60	Bottom of right atrium	AV nodal delay
AV bundle	30-40	Ventricular septum	
Bundle branches	20-30	Ventricular septum	
Purkinje fibers	15-20	Throughout myocardium	

Firing Rates for Conduction Fibers

Electrocardiogram

By careful placement of surface electrodes on the body, it is possible to record the complex, compound electrical signal of the heart. This tracing of the electrical signal is the **electrocardiogram (ECG)**, also commonly abbreviated EKG (K coming kardiology, from the German term for cardiology). Careful analysis of the ECG reveals a detailed picture of both normal and abnormal heart function, and is an indispensable clinical diagnostic tool. The standard electrocardiograph (the instrument that generates an ECG) uses 3, 5, or 12 leads. The greater the number of leads an electrocardiograph uses, the more information the ECG provides. The term "lead" may be used to refer to the cable from the electrode to the electrical recorder, but it typically describes the voltage difference between two of the electrodes. The 12-lead electrocardiograph uses 10 electrodes placed in standard locations on the patient's skin ([link]). In continuous ambulatory electrocardiographs, the patient wears a small, portable, batteryoperated device known as a Holter monitor, or simply a Holter, that continuously monitors heart electrical activity, typically for a period of 24 hours during the patient's normal routine.

Standard Placement of ECG Leads



In a 12-lead ECG, six electrodes are placed on the chest, and four electrodes are placed on the limbs.

A normal ECG tracing is presented in [link]. Each component, segment, and interval is labeled and corresponds to important electrical events, demonstrating the relationship between these events and contraction in the heart.

There are five prominent points on the ECG: the P wave, the QRS complex, and the T wave. The small **P** wave represents the depolarization of the atria. The atria begin contracting approximately 25 ms after the start of the P wave. The large **QRS complex** represents the depolarization of the ventricles, which requires a much stronger electrical signal because of the larger size of the ventricular cardiac muscle. The ventricles begin to contract as the QRS reaches the peak of the R wave. Lastly, the **T** wave represents the repolarization of the ventricles. The repolarization of the atria occurs during the QRS complex, which masks it on an ECG.

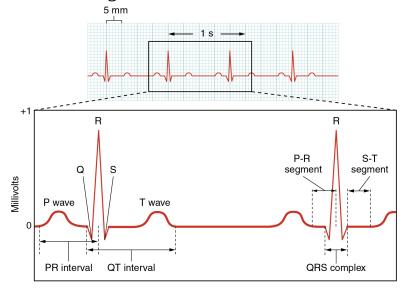
The major segments and intervals of an ECG tracing are indicated in [link]. Segments are defined as the regions between two waves. Intervals include one segment plus one or more waves. For example, the PR segment begins at the end of the P wave and ends at the beginning of the QRS complex. The PR interval starts at the beginning of the P wave and ends with the beginning of the QRS complex. The PR interval is more clinically relevant, as it measures the duration from the beginning of atrial depolarization (the P wave) to the initiation of the QRS complex. Since the Q wave may be difficult to view in some tracings, the measurement is often extended to the R that is more easily visible. Should there be a delay in passage of the impulse from the SA node to the AV node, it would be visible in the PR interval. [link] correlates events of heart contraction to the corresponding segments and intervals of an ECG.

Note:



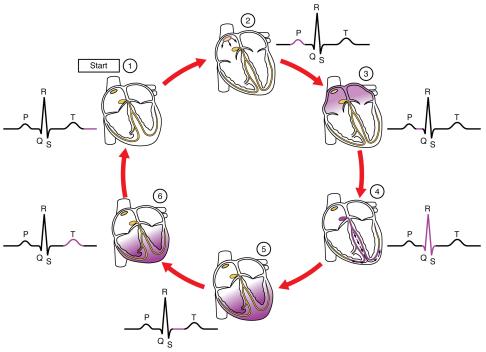
Visit this <u>site</u> for a more detailed analysis of ECGs.

Electrocardiogram



A normal tracing shows the P wave, QRS complex, and T wave. Also indicated are the PR, QT, QRS, and ST intervals, plus the P-R and S-T segments.

ECG Tracing Correlated to the Cardiac Cycle



This diagram correlates an ECG tracing with the electrical and mechanical events of a heart contraction. Each segment of an ECG tracing corresponds to one event in the cardiac cycle.

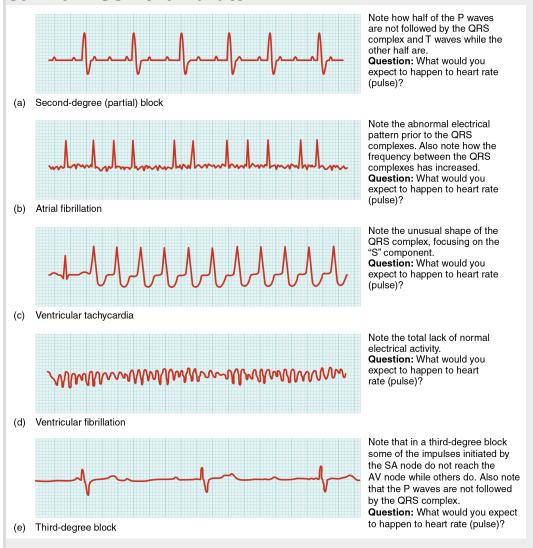
Note:

Everyday Connection ECG Abnormalities

Occassionally, an area of the heart other than the SA node will initiate an impulse that will be followed by a premature contraction. Such an area, which may actually be a component of the conduction system or some other contractile cells, is known as an ectopic focus or ectopic pacemaker. An ectopic focus may be stimulated by localized ischemia; exposure to certain drugs, including caffeine, digitalis, or acetylcholine; elevated stimulation by both sympathetic or parasympathetic divisions of the autonomic nervous system; or a number of disease or pathological conditions. Occasional occurances are generally transitory and nonlife threatening, but if the condition becomes chronic, it may lead to either an arrhythmia, a deviation from the normal pattern of impulse conduction and contraction, or to fibrillation, an uncoordinated beating of the heart. While interpretation of an ECG is possible and extremely valuable after some training, a full understanding of the complexities and intricacies generally requires several years of experience. In general, the size of the electrical variations, the duration of the events, and detailed vector analysis provide the most comprehensive picture of cardiac function. For example, an amplified P wave may indicate enlargement of the atria, an enlarged Q wave may indicate a MI, and an enlarged suppressed or inverted Q wave often indicates enlarged ventricles. T waves often appear flatter when insufficient oxygen is being delivered to the myocardium. An elevation of the ST segment above baseline is often seen in patients with an acute MI, and may appear depressed below the baseline when hypoxia is occurring. As useful as analyzing these electrical recordings may be, there are limitations. For example, not all areas suffering a MI may be obvious on

the ECG. Additionally, it will not reveal the effectiveness of the pumping, which requires further testing, such as an ultrasound test called an echocardiogram or nuclear medicine imaging. It is also possible for there to be pulseless electrical activity, which will show up on an ECG tracing, although there is no corresponding pumping action. Common abnormalities that may be detected by the ECGs are shown in [link].





(a) In a second-degree or partial block, one-half of the P waves are not followed by the QRS complex and T waves while the other half are. (b) In atrial fibrillation, the electrical pattern is abnormal prior to the QRS complex, and the frequency between the QRS complexes has increased. (c) In ventricular tachycardia, the shape of the

QRS complex is abnormal. (d) In ventricular fibrillation, there is no normal electrical activity. (e) In a third-degree block, there is no correlation between atrial activity (the P wave) and ventricular activity (the QRS complex).

Note:



Visit this <u>site</u> for a more complete library of abnormal ECGs.

Note:

Everyday Connection

External Automated Defibrillators

In the event that the electrical activity of the heart is severely disrupted, cessation of electrical activity or fibrillation may occur. In fibrillation, the heart beats in a wild, uncontrolled manner, which prevents it from being able to pump effectively. Atrial fibrillation (see [link]b) is a serious condition, but as long as the ventricles continue to pump blood, the patient's life may not be in immediate danger. Ventricular fibrillation (see [link]d) is a medical emergency that requires life support, because the ventricles are not effectively pumping blood. In a hospital setting, it is often described as "code blue." If untreated for as little as a few minutes, ventricular fibrillation may lead to brain death. The most common treatment is defibrillation, which uses special paddles to apply a charge to the heart from an external electrical source in an attempt to establish a normal sinus rhythm ([link]). A defibrillator effectively stops the heart so

that the SA node can trigger a normal conduction cycle. Because of their effectiveness in reestablishing a normal sinus rhythm, external automated defibrillators (EADs) are being placed in areas frequented by large numbers of people, such as schools, restaurants, and airports. These devices contain simple and direct verbal instructions that can be followed by nonmedical personnel in an attempt to save a life.

Defibrillators



(a) An external automatic defibrillator can be used by nonmedical personnel to reestablish a normal sinus rhythm in a person with fibrillation. (b) Defibrillator paddles are more commonly used in hospital settings. (credit b: "widerider107"/flickr.com)

A **heart block** refers to an interruption in the normal conduction pathway. The nomenclature for these is very straightforward. SA nodal blocks occur within the SA node. AV nodal blocks occur within the AV node. Infra-Hisian blocks involve the bundle of His. Bundle branch blocks occur within either the left or right atrioventricular bundle branches. Hemiblocks are partial and occur within one or more fascicles of the atrioventricular bundle branch. Clinically, the most common types are the AV nodal and infra-Hisian blocks.

AV blocks are often described by degrees. A first-degree or partial block indicates a delay in conduction between the SA and AV nodes. This can be recognized on the ECG as an abnormally long PR interval. A second-degree or incomplete block occurs when some impulses from the SA node reach the AV node and continue, while others do not. In this instance, the ECG would reveal some P waves not followed by a QRS complex, while others would appear normal. In the third-degree or complete block, there is no correlation between atrial activity (the P wave) and ventricular activity (the QRS complex). Even in the event of a total SA block, the AV node will assume the role of pacemaker and continue initiating contractions at 40–60 contractions per minute, which is adequate to maintain consciousness. Second- and third-degree blocks are demonstrated on the ECG presented in [link].

When arrhythmias become a chronic problem, the heart maintains a junctional rhythm, which originates in the AV node. In order to speed up the heart rate and restore full sinus rhythm, a cardiologist can implant an **artificial pacemaker**, which delivers electrical impulses to the heart muscle to ensure that the heart continues to contract and pump blood effectively. These artificial pacemakers are programmable by the cardiologists and can either provide stimulation temporarily upon demand or on a continuous basis. Some devices also contain built-in defibrillators.

Cardiac Muscle Metabolism

Normally, cardiac muscle metabolism is entirely aerobic. Oxygen from the lungs is brought to the heart, and every other organ, attached to the hemoglobin molecules within the erythrocytes. Heart cells also store appreciable amounts of oxygen in myoglobin. Normally, these two mechanisms, circulating oxygen and oxygen attached to myoglobin, can supply sufficient oxygen to the heart, even during peak performance.

Fatty acids and glucose from the circulation are broken down within the mitochondria to release energy in the form of ATP. Both fatty acid droplets and glycogen are stored within the sarcoplasm and provide additional nutrient supply. (Seek additional content for more detail about metabolism.)

Chapter Review

The heart is regulated by both neural and endocrine control, yet it is capable of initiating its own action potential followed by muscular contraction. The conductive cells within the heart establish the heart rate and transmit it through the myocardium. The contractile cells contract and propel the blood. The normal path of transmission for the conductive cells is the sinoatrial (SA) node, internodal pathways, atrioventricular (AV) node, atrioventricular (AV) bundle of His, bundle branches, and Purkinje fibers. The action potential for the conductive cells consists of a prepotential phase with a slow influx of Na⁺ followed by a rapid influx of Ca²⁺ and outflux of K⁺. Contractile cells have an action potential with an extended plateau phase that results in an extended refractory period to allow complete contraction for the heart to pump blood effectively. Recognizable points on the ECG include the P wave that corresponds to atrial depolarization, the QRS complex that corresponds to ventricular depolarization, and the T wave that corresponds to ventricular repolarization.

Chapter Review

The heart is regulated by both neural and endocrine control, yet it is capable of initiating its own action potential followed by muscular contraction. The pacemaker cells within the heart establish the heart rate and transmit it through the myocardium. The contractile cells contract and propel the blood. The normal path of transmission for the pacemaker cells is the sinoatrial (SA) node, internodal pathways, atrioventricular (AV) node, atrioventricular (AV) bundle of His, bundle branches, and Purkinje fibers. The pacemaker cells produce a pacemaker potential that is represented by a slow depolarization phase. Once threshold is reached, an action potential will follow. Contractile cells have an action potential with an extended plateau phase that results in an extended refractory period to allow complete contraction for the heart to pump blood effectively. Recognizable points on the ECG include the P wave that corresponds to atrial depolarization, the QRS complex that corresponds to ventricular depolarization, and the T wave that corresponds to ventricular repolarization.

Glossary

artificial pacemaker

medical device that transmits electrical signals to the heart to ensure that it contracts and pumps blood to the body

atrioventricular bundle

(also, bundle of His) group of specialized myocardial conductile cells that transmit the impulse from the AV node through the interventricular septum; form the left and right atrioventricular bundle branches

atrioventricular bundle branches

(also, left or right bundle branches) specialized myocardial conductile cells that arise from the bifurcation of the atrioventricular bundle and pass through the interventricular septum; lead to the Purkinje fibers and also to the right papillary muscle via the moderator band

atrioventricular (AV) node

clump of myocardial cells located in the inferior portion of the right atrium within the atrioventricular septum; receives the impulse from the SA node, pauses, and then transmits it into specialized conducting cells within the interventricular septum

autorhythmicity

ability of cardiac muscle to initiate its own electrical impulse that triggers the mechanical contraction that pumps blood at a fixed pace without nervous or endocrine control

bundle of His

(also, atrioventricular bundle) group of specialized myocardial conductile cells that transmit the impulse from the AV node through the interventricular septum; form the left and right atrioventricular bundle branches

electrocardiogram (ECG)

surface recording of the electrical activity of the heart that can be used for diagnosis of irregular heart function; also abbreviated as EKG

heart block

interruption in the normal conduction pathway

interatrial band

(also, Bachmann's bundle) group of specialized conducting cells that transmit the impulse directly from the SA node in the right atrium to the left atrium

intercalated disc

physical junction between adjacent cardiac muscle cells; consisting of desmosomes, specialized linking proteoglycans, and gap junctions that allow passage of ions between the two cells

interarterial pathway

(also, Bachmann's bundle) group of specialized conducting cells that transmit the impulse directly from the SA node in the right atrium to the left atrium

internodal pathways

specialized conductile cells within the atria that transmit the impulse from the SA node throughout the myocardial cells of the atrium and to the AV node

P wave

component of the electrocardiogram that represents the depolarization of the atria

pacemaker

cluster of specialized myocardial cells known as the SA node that initiates the sinus rhythm

Purkinje fibers

specialized myocardial conduction fibers that arise from the bundle branches and spread the impulse to the myocardial contraction fibers of the ventricles

QRS complex

component of the electrocardiogram that represents the depolarization of the ventricles and includes, as a component, the repolarization of the atria

sinoatrial (SA) node

known as the pacemaker, a specialized clump of myocardial conducting cells located in the superior portion of the right atrium that has the highest inherent rate of depolarization that then spreads throughout the heart

sinus rhythm

normal contractile pattern of the heart

T wave

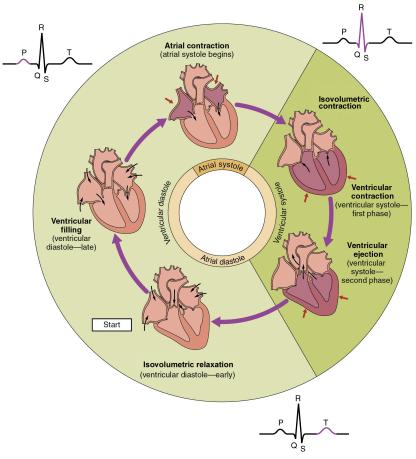
component of the electrocardiogram that represents the repolarization of the ventricles

OU Human Physiology: Cardiac Cycle By the end of this section, you will be able to:

• Describe the correlation between the phases of systole and diastole, heart valves, heart sounds, ECG, and aortic, ventricular, and atrial pressure and volumes in the cardiac cycle

The period of time that begins with contraction of the atria and ends with ventricular relaxation is known as the **cardiac cycle** ([link]). The period of contraction that the heart undergoes while it pumps blood into circulation is called **systole**. The period of relaxation that occurs as the chambers fill with blood is called **diastole**. Both the atria and ventricles undergo systole and diastole, and it is essential that these components be carefully regulated and coordinated to ensure blood is pumped efficiently to the body.

Overview of the Cardiac Cycle



The cardiac cycle begins with atrial systole and

progresses to ventricular systole, atrial diastole, and ventricular diastole, when the cycle begins again. Correlations to the ECG are highlighted.

Pressures and Flow

Fluids, whether gases or liquids, are materials that flow according to pressure gradients—that is, they move from regions that are higher in pressure to regions that are lower in pressure. Accordingly, when the heart chambers are relaxed (diastole), blood will flow into the atria from the veins, which are higher in pressure. As blood flows into the atria, the pressure will rise, so the blood will initially move passively from the atria into the ventricles. When the action potential triggers the muscles in the atria to contract (atrial systole), the pressure within the atria rises further, pumping blood into the ventricles. During ventricular systole, pressure rises in the ventricles, pumping blood into the pulmonary trunk from the right ventricle and into the aorta from the left ventricle. Again, as you consider this flow and relate it to the conduction pathway, the elegance of the system should become apparent.

Phases of the Cardiac Cycle

At the beginning of the cardiac cycle, both the atria and ventricles are relaxed (diastole). Blood is flowing into the right atrium from the superior and inferior venae cavae and the coronary sinus. Blood flows into the left atrium from the pulmonary veins. The two atrioventricular valves, the tricuspid and mitral valves, are both open, so blood flows unimpeded from the atria and into the ventricles. Approximately 70–80 percent of ventricular filling occurs by this method. The two semilunar valves, the pulmonary and aortic valves, are closed, preventing backflow of blood into the right and left ventricles from the pulmonary trunk on the right and the aorta on the left.

Atrial Systole and Diastole

Contraction of the atria follows depolarization, represented by the P wave of the ECG. As the atrial muscles contract from the superior portion of the atria toward the atrioventricular septum, pressure rises within the atria and blood is pumped into the ventricles through the open atrioventricular (tricuspid, and mitral or bicuspid) valves. At the start of atrial systole, the ventricles are normally filled with approximately 70–80 percent of their capacity due to inflow during diastole. Atrial contraction, also referred to as the "atrial kick," contributes the remaining 20–30 percent of filling (see [link]). Atrial systole lasts approximately 100 ms and ends prior to ventricular systole, as the atrial muscle returns to diastole.

Ventricular Systole

Ventricular systole (see [link]) follows the depolarization of the ventricles and is represented by the QRS complex in the ECG. It may be conveniently divided into two phases, lasting a total of 270 ms. At the end of atrial systole and just prior to atrial contraction, the ventricles contain approximately 130 mL blood in a resting adult in a standing position. This volume is known as the **end diastolic volume (EDV)** or **preload**.

Initially, as the muscles in the ventricle contract, the pressure of the blood within the chamber rises, but it is not yet high enough to open the semilunar (pulmonary and aortic) valves and be ejected from the heart. However, blood pressure quickly rises above that of the atria that are now relaxed and in diastole. This increase in pressure causes blood to flow back toward the atria, closing the tricuspid and mitral valves. Since blood is not being ejected from the ventricles at this early stage, the volume of blood within the chamber remains constant. Consequently, this initial phase of ventricular systole is known as **isovolumetric contraction** (see [link]).

In the second phase of ventricular systole, the **ventricular ejection phase**, the contraction of the ventricular muscle has raised the pressure within the ventricle to the point that it is greater than the pressures in the pulmonary trunk and the aorta. Blood is pumped from the heart, pushing open the

pulmonary and aortic semilunar valves. Pressure generated by the left ventricle will be appreciably greater than the pressure generated by the right ventricle, since the existing pressure in the aorta will be so much higher. Nevertheless, both ventricles pump the same amount of blood. This quantity is referred to as stroke volume. Stroke volume will normally be in the range of 70–80 mL. Since ventricular systole began with an EDV of approximately 130 mL of blood, this means that there is still 50–60 mL of blood remaining in the ventricle following contraction. This volume of blood is known as the **end systolic volume (ESV)**.

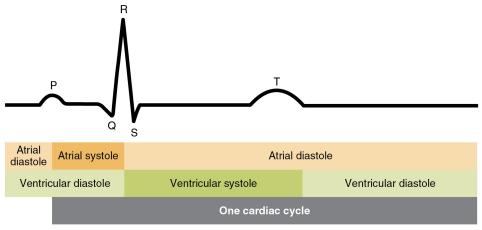
Ventricular Diastole

Ventricular relaxation, or diastole, follows repolarization of the ventricles and is represented by the T wave of the ECG. It too is divided into two distinct phases and lasts approximately 430 ms.

During the early phase of ventricular diastole, as the ventricular muscle relaxes, pressure on the remaining blood within the ventricle begins to fall. When pressure within the ventricles drops below pressure in both the pulmonary trunk and aorta, blood flows back toward the heart, producing the dicrotic notch (small dip) seen in blood pressure tracings. The semilunar valves close to prevent backflow into the heart. Since the atrioventricular valves remain closed at this point, there is no change in the volume of blood in the ventricle, so the early phase of ventricular diastole is called the **isovolumetric ventricular relaxation phase** (see [link]).

In the second phase of ventricular diastole, called late ventricular diastole, as the ventricular muscle relaxes, pressure on the blood within the ventricles drops even further. Eventually, it drops below the pressure in the atria. When this occurs, blood flows from the atria into the ventricles, pushing open the tricuspid and mitral valves. As pressure drops within the ventricles, blood flows from the major veins into the relaxed atria and from there into the ventricles. Both chambers are in diastole, the atrioventricular valves are open, and the semilunar valves remain closed (see [link]). The cardiac cycle is complete.

[link] illustrates the relationship between the cardiac cycle and the ECG. Relationship between the Cardiac Cycle and ECG



Initially, both the atria and ventricles are relaxed (diastole). The P wave represents depolarization of the atria and is followed by atrial contraction (systole). Atrial systole extends until the QRS complex, at which point, the atria relax. The QRS complex represents depolarization of the ventricles and is followed by ventricular contraction. The T wave represents the repolarization of the ventricles and marks the beginning of ventricular relaxation.

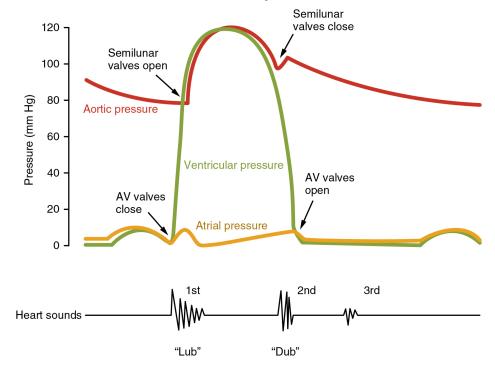
Heart Sounds

One of the simplest, yet effective, diagnostic techniques applied to assess the state of a patient's heart is auscultation using a stethoscope.

In a normal, healthy heart, there are only two audible **heart sounds**: S_1 and S_2 . S_1 is the sound created by the closing of the atrioventricular valves during ventricular contraction and is normally described as a "lub," or first heart sound. The second heart sound, S_2 , is the sound of the closing of the semilunar valves during ventricular diastole and is described as a "dub" ([link]). In both cases, as the valves close, the openings within the atrioventricular septum guarded by the valves will become reduced, and

blood flow through the opening will become more turbulent until the valves are fully closed. There is a third heart sound, S_3 , but it is rarely heard in healthy individuals. It may be the sound of blood flowing into the atria, or blood sloshing back and forth in the ventricle, or even tensing of the chordae tendineae. S_3 may be heard in youth, some athletes, and pregnant women. If the sound is heard later in life, it may indicate congestive heart failure, warranting further tests. Some cardiologists refer to the collective S_1 , S_2 , and S_3 sounds as the "Kentucky gallop," because they mimic those produced by a galloping horse. The fourth heart sound, S_4 , results from the contraction of the atria pushing blood into a stiff or hypertrophic ventricle, indicating failure of the left ventricle. S_4 occurs prior to S_1 and the collective sounds S_4 , S_1 , and S_2 are referred to by some cardiologists as the "Tennessee gallop," because of their similarity to the sound produced by a galloping horse with a different gait. A few individuals may have both S_3 and S_4 , and this combined sound is referred to as S_7 .

Heart Sounds and the Cardiac Cycle

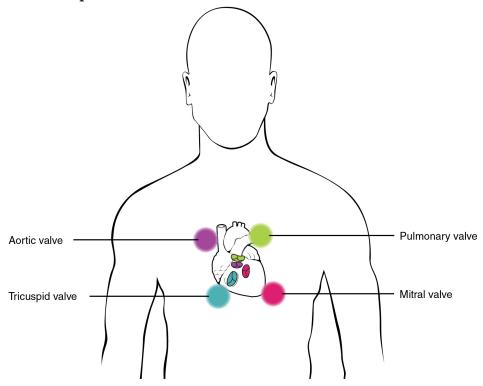


In this illustration, the x-axis reflects time with a recording of the heart sounds. The y-axis represents pressure.

The term **murmur** is used to describe an unusual sound coming from the heart that is caused by the turbulent flow of blood. Murmurs are graded on a scale of 1 to 6, with 1 being the most common, the most difficult sound to detect, and the least serious. The most severe is a 6. Phonocardiograms or auscultograms can be used to record both normal and abnormal sounds using specialized electronic stethoscopes.

During auscultation, it is common practice for the clinician to ask the patient to breathe deeply. This procedure not only allows for listening to airflow, but it may also amplify heart murmurs. Inhalation increases blood flow into the right side of the heart and may increase the amplitude of right-sided heart murmurs. Expiration partially restricts blood flow into the left side of the heart and may amplify left-sided heart murmurs. [link] indicates proper placement of the bell of the stethoscope to facilitate auscultation.

Stethoscope Placement for Auscultation



Proper placement of the bell of the stethoscope facilitates auscultation. At each of the four locations on the chest, a different valve can be heard.

Chapter Review

The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract (atrial systole), following depolarization of the atria, and pump blood into the ventricles. The ventricles begin to contract (ventricular systole), raising pressure within the ventricles. When ventricular pressure rises above the pressure in the atria, blood flows toward the atria, producing the first heart sound, S_1 or lub. As pressure in the ventricles rises above two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax (ventricular diastole), and pressure within the ventricles drops. As ventricular pressure drops, there is a tendency for blood to flow back into the atria from the major arteries, producing the dicrotic notch in the ECG and closing the two semilunar valves. The second heart sound, S_2 or dub, occurs when the semilunar valves close. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle. The valves prevent backflow of blood. Failure of the valves to operate properly produces turbulent blood flow within the heart; the resulting heart murmur can often be heard with a stethoscope.

Chapter Review

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Glossary

cardiac cycle

period of time between the onset of atrial contraction (atrial systole) and ventricular relaxation (ventricular diastole)

diastole

period of time when the heart muscle is relaxed and the chambers fill with blood

end diastolic volume (EDV)

(also, preload) the amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

end systolic volume (ESV)

amount of blood remaining in each ventricle following systole

heart sounds

sounds heard via auscultation with a stethoscope of the closing of the atrioventricular valves ("lub") and semilunar valves ("dub")

isovolumic contraction

(also, isovolumetric contraction) initial phase of ventricular contraction in which tension and pressure in the ventricle increase, but no blood is pumped or ejected from the heart

isovolumic ventricular relaxation phase

initial phase of the ventricular diastole when pressure in the ventricles drops below pressure in the two major arteries, the pulmonary trunk, and the aorta, and blood attempts to flow back into the ventricles, producing the dicrotic notch of the ECG and closing the two semilunar valves

murmur

unusual heart sound detected by auscultation; typically related to septal or valve defects

preload

(also, end diastolic volume) amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

systole

period of time when the heart muscle is contracting

ventricular ejection phase

second phase of ventricular systole during which blood is pumped from the ventricle

OU Human Physiology: Cardiac Physiology By the end of this section, you will be able to:

- Describe how altering heart rate and/or stroke volume will alter cardiac output
- Identify and describe the cardiovascular centers and cardiac reflex centers that regulate function
- Describe factors affecting heart rate
- Distinguish between positive and negative factors that affect heart contractility
- Explain the factors that alter stroke volume, heart rate, and how those factors will alter cardiac output
- Describe the cardiac response to variations in blood flow and pressure
- Compare and contrast parasympathetic and sympathetic innervation to the heart
- Describe the mechanism that increases heart rate via the sympathetic nervous system
- Describe the mechanism that decreases heart rate via the parasympathetic nervous system
- Discuss the factors that increase and decrease heart rate as well as force of contraction

The autorhythmicity inherent in cardiac cells keeps the heart beating at a regular pace; however, the heart is regulated by and responds to outside influences as well. Neural and endocrine controls are vital to the regulation of cardiac function. In addition, the heart is sensitive to several environmental factors, including electrolytes.

Resting Cardiac Output

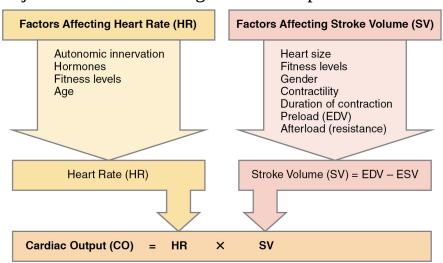
Cardiac output (CO) is a measurement of the amount of blood pumped by each ventricle in one minute. To calculate this value, multiply **stroke volume (SV)**, the amount of blood pumped by each ventricle, by **heart rate (HR)**, in contractions per minute (or beats per minute, bpm). It can be represented mathematically by the following equation:

 $CO = HR \times SV$

SV is normally measured using an echocardiogram to record EDV and ESV, and calculating the difference: SV = EDV – ESV. SV can also be measured using a specialized catheter, but this is an invasive procedure and far more dangerous to the patient. A mean SV for a resting 70-kg (150-lb) individual would be approximately 70 mL. There are several important variables, including size of the heart, physical and mental condition of the individual, sex, contractility, duration of contraction, preload or EDV, and afterload or resistance. Normal range for SV would be 55–100 mL. An average resting HR would be approximately 75 bpm but could range from 60–100 in some individuals.

Using these numbers, the mean CO is 5.25 L/min, with a range of 4.0–8.0 L/min. Remember, however, that these numbers refer to CO from each ventricle separately, not the total for the heart. Factors influencing CO are summarized in [link].

Major Factors Influencing Cardiac Output



Cardiac output is influenced by heart rate and stroke volume, both of which are also variable.

SVs are also used to calculate **ejection fraction**, which is the portion of the blood that is pumped or ejected from the heart with each contraction. To calculate ejection fraction, SV is divided by EDV. Despite the name, the

ejection fraction is normally expressed as a percentage. Ejection fractions range from approximately 55–70 percent, with a mean of 58 percent.

Exercise and Maximum Cardiac Output

In healthy young individuals, HR may increase to 150 bpm during exercise. SV can also increase from 70 to approximately 130 mL due to increased strength of contraction. This would increase CO to approximately 19.5 L/min, 4–5 times the resting rate. Top cardiovascular athletes can achieve even higher levels. At their peak performance, they may increase resting CO by 7–8 times.

Since the heart is a muscle, exercising it increases its efficiency. The difference between maximum and resting CO is known as the **cardiac reserve**. It measures the residual capacity of the heart to pump blood.

Heart Rates

HRs vary considerably, not only with exercise and fitness levels, but also with age. Newborn resting HRs may be 120 bpm. HR gradually decreases until young adulthood and then gradually increases again with age.

Maximum HRs are normally in the range of 200–220 bpm, although there are some extreme cases in which they may reach higher levels. As one ages, the ability to generate maximum rates decreases. This may be estimated by taking the maximal value of 220 bpm and subtracting the individual's age. So a 40-year-old individual would be expected to hit a maximum rate of approximately 180, and a 60-year-old person would achieve a HR of 160.

Note:

Disorders of the...

Heart: Abnormal Heart Rates

For an adult, normal resting HR will be in the range of 60–100 bpm. Bradycardia is the condition in which resting rate drops below 60 bpm, and tachycardia is the condition in which the resting rate is above 100 bpm.

Trained athletes typically have very low HRs. If the patient is not exhibiting other symptoms, such as weakness, fatigue, dizziness, fainting, chest discomfort, palpitations, or respiratory distress, bradycardia is not considered clinically significant. However, if any of these symptoms are present, they may indicate that the heart is not providing sufficient oxygenated blood to the tissues. The term relative bradycardia may be used with a patient who has a HR in the normal range but is still suffering from these symptoms. Most patients remain asymptomatic as long as the HR remains above 50 bpm.

Bradycardia may be caused by either inherent factors or causes external to the heart. While the condition may be inherited, typically it is acquired in older individuals. Inherent causes include abnormalities in either the SA or AV node. If the condition is serious, a pacemaker may be required. Other causes include ischemia to the heart muscle or diseases of the heart vessels or valves. External causes include metabolic disorders, pathologies of the endocrine system often involving the thyroid, electrolyte imbalances, neurological disorders including inappropriate autonomic responses, autoimmune pathologies, over-prescription of beta blocker drugs that reduce HR, recreational drug use, or even prolonged bed rest. Treatment relies upon establishing the underlying cause of the disorder and may necessitate supplemental oxygen.

Tachycardia is not normal in a resting patient but may be detected in pregnant women or individuals experiencing extreme stress. In the latter case, it would likely be triggered by stimulation from the limbic system or disorders of the autonomic nervous system. In some cases, tachycardia may involve only the atria. Some individuals may remain asymptomatic, but when present, symptoms may include dizziness, shortness of breath, lightheadedness, rapid pulse, heart palpations, chest pain, or fainting (syncope). While tachycardia is defined as a HR above 100 bpm, there is considerable variation among people. Further, the normal resting HRs of children are often above 100 bpm, but this is not considered to be tachycardia Many causes of tachycardia may be benign, but the condition may also be correlated with fever, anemia, hypoxia, hyperthyroidism, hypersecretion of catecholamines, some cardiomyopathies, some disorders of the valves, and acute exposure to radiation. Elevated rates in an exercising or resting patient are normal and expected. Resting rate should always be taken after recovery from exercise. Treatment depends upon the

underlying cause but may include medications, implantable cardioverter defibrillators, ablation, or surgery.

Correlation Between Heart Rate and Cardiac Output

Initially, physiological conditions that cause HR to increase also trigger an increase in SV. During exercise, the rate of blood returning to the heart increases. However as the HR rises, there is less time spent in diastole and consequently less time for the ventricles to fill with blood. Even though there is less filling time, SV will initially remain high. However, as HR continues to increase, SV gradually decreases due to decreased filling time. CO will initially stabilize as the increasing HR compensates for the decreasing SV, but at very high rates, CO will eventually decrease as increasing rates are no longer able to compensate for the decreasing SV. Consider this phenomenon in a healthy young individual. Initially, as HR increases from resting to approximately 120 bpm, CO will rise. As HR increases from 120 to 160 bpm, CO remains stable, since the increase in rate is offset by decreasing ventricular filling time and, consequently, SV. As HR continues to rise above 160 bpm, CO actually decreases as SV falls faster than HR increases. So although aerobic exercises are critical to maintain the health of the heart, individuals are cautioned to monitor their HR to ensure they stay within the **target heart rate** range of between 120 and 160 bpm, so CO is maintained. The target HR is loosely defined as the range in which both the heart and lungs receive the maximum benefit from the aerobic workout and is dependent upon age.

Cardiovascular Centers

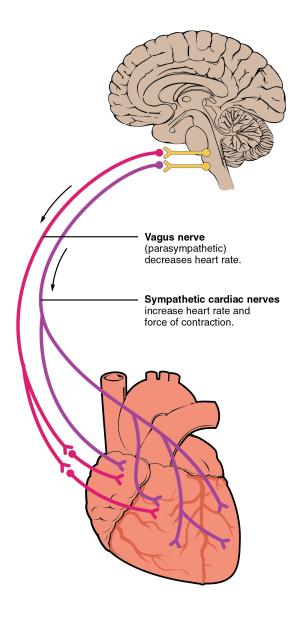
Nervous control over HR is centralized within the two paired cardiovascular centers of the medulla oblongata ([link]). The cardioaccelerator regions stimulate activity via sympathetic stimulation of the cardioaccelerator nerves, and the cardioinhibitory centers decrease heart activity via parasympathetic stimulation as one component of the vagus nerve, cranial nerve X. During rest, both centers provide slight stimulation to the heart, contributing to **autonomic tone**. This is a similar concept to

tone in skeletal muscles. Normally, vagal stimulation predominates as, left unregulated, the SA node would initiate a sinus rhythm of approximately 100 bpm.

Both sympathetic and parasympathetic stimulations flow through a paired complex network of nerve fibers known as the **cardiac plexus** near the base of the heart. The cardioaccelerator center also sends additional fibers, forming the cardiac nerves via sympathetic ganglia to both the SA and AV nodes, plus additional fibers to the atria and ventricles. The ventricles are more richly innervated by sympathetic fibers than parasympathetic fibers. Sympathetic stimulation causes the release of the neurotransmitter norepinephrine (NE) and epinephrine (E) at the neuromuscular junction of the cardiac nerves. NE/E bind to β_1 adrenergic receptors in the SA/AV nodes and ventricular myocardium. Binding stimulates the cAMP second messenger system which activates protein kinase A which phosphorylates the Na⁺ channel and voltage-gated L-type Ca²⁺ causing them to open which causes a faster pacemaker potential. This will cause voltage-gated K⁺ channels to close sooner which will result in a shortened repolarization phase in the pacemaker cell. This will increase the frequency of pacemaker potentials which will increase heart rate.

NE binds to the beta-1 receptor. Some cardiac medications (for example, beta blockers) work by blocking these receptors, thereby slowing HR and are one possible treatment for hypertension. Overprescription of these drugs may lead to bradycardia and even stoppage of the heart.

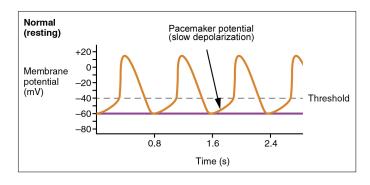
Autonomic Innervation of the Heart

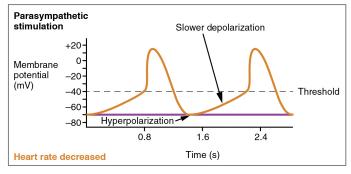


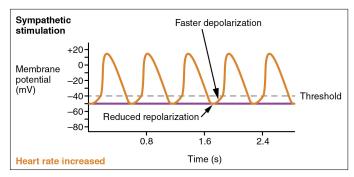
Cardioaccelerator and cardioinhibitory areas are components of the paired cardiac centers located in the medulla oblongata of the brain. They innervate the heart via sympathetic cardiac nerves that increase cardiac activity and vagus (parasympathetic) nerves that slow cardiac activity.

Parasympathetic stimulation originates from the cardioinhibitory region with impulses traveling via the vagus nerve (cranial nerve X). The vagus nerve sends branches to both the SA and AV nodes, and to portions of both the atria and ventricles. Parasympathetic stimulation releases the neurotransmitter acetylcholine (ACh) at the neuromuscular junction. ACh will bind to muscarinic cholinergic receptors in the SA and AV nodes. Binding stimulates direct coupling to occur. The α-subunit of the G protein opens the voltage-gated K⁺ channels to slow the rate of slow depolarization and extends repolarization by delaying the Na⁺ and voltage-gated T-type Ca²⁺ channels. Together these will increase the time before the next spontaneous depolarization occurs. Without any nervous stimulation, the SA node would establish a sinus rhythm of approximately 100 bpm. Since resting rates are considerably less than this, it becomes evident that parasympathetic stimulation normally slows HR. This is similar to an individual driving a car with one foot on the brake pedal. To speed up, one need merely remove one's foot from the break and let the engine increase speed. In the case of the heart, decreasing parasympathetic stimulation decreases the release of ACh, which allows HR to increase up to approximately 100 bpm. Any increases beyond this rate would require sympathetic stimulation. [link] illustrates the effects of parasympathetic and sympathetic stimulation on the normal sinus rhythm.

Effects of Parasympathetic and Sympathetic Stimulation on Normal Sinus Rhythm







The wave of depolarization in a normal sinus rhythm shows a stable resting HR. Following parasympathetic stimulation, HR slows. Following sympathetic stimulation, HR increases.

Input to the Cardiovascular Center

The cardiovascular center receives input from a series of visceral receptors with impulses traveling through visceral sensory fibers within the vagus and

sympathetic nerves via the cardiac plexus. Among these receptors are various proprioreceptors, baroreceptors, and chemoreceptors, plus stimuli from the limbic system. Collectively, these inputs normally enable the cardiovascular centers to regulate heart function precisely, a process known as **cardiac reflexes**. Increased physical activity results in increased rates of firing by various proprioreceptors located in muscles, joint capsules, and tendons. Any such increase in physical activity would logically warrant increased blood flow. The cardiac centers monitor these increased rates of firing, and suppress parasympathetic stimulation and increase sympathetic stimulation as needed in order to increase blood flow.

Similarly, baroreceptors are stretch receptors located in the aortic sinus, carotid bodies, the venae cavae, and other locations, including pulmonary vessels and the right side of the heart itself. Rates of firing from the baroreceptors represent blood pressure, level of physical activity, and the relative distribution of blood. The cardiac centers monitor baroreceptor firing to maintain cardiac homeostasis, a mechanism called the **baroreceptor reflex**. With increased pressure and stretch, the rate of baroreceptor firing increases, and the cardiac centers decrease sympathetic stimulation and increase parasympathetic stimulation. As pressure and stretch decrease, the rate of baroreceptor firing decreases, and the cardiac centers increase sympathetic stimulation and decrease parasympathetic stimulation.

There is a similar reflex, called the atrial reflex or Bainbridge reflex, associated with varying rates of blood flow to the atria. Increased venous return stretches the walls of the atria where specialized baroreceptors are located. However, as the atrial baroreceptors increase their rate of firing and as they stretch due to the increased blood pressure, the cardiac center responds by increasing sympathetic stimulation and inhibiting parasympathetic stimulation to increase HR. The opposite is also true.

Increased metabolic byproducts associated with increased activity, such as carbon dioxide, hydrogen ions, and lactic acid, plus falling oxygen levels, are detected by a suite of chemoreceptors innervated by the glossopharyngeal and vagus nerves. These chemoreceptors provide

feedback to the cardiovascular centers about the need for increased or decreased blood flow, based on the relative levels of these substances.

The limbic system can also significantly impact HR related to emotional state. During periods of stress, it is not unusual to identify higher than normal HRs, often accompanied by a surge in the stress hormone cortisol. Individuals experiencing extreme anxiety may manifest panic attacks with symptoms that resemble those of heart attacks. These events are typically transient and treatable. Meditation techniques have been developed to ease anxiety and have been shown to lower HR effectively. Doing simple deep and slow breathing exercises with one's eyes closed can also significantly reduce this anxiety and HR.

Note:

Disorders of the...

Heart: Broken Heart Syndrome

Extreme stress from such life events as the death of a loved one, an emotional break up, loss of income, or foreclosure of a home may lead to a condition commonly referred to as broken heart syndrome. This condition may also be called Takotsubo cardiomyopathy, transient apical ballooning syndrome, apical ballooning cardiomyopathy, stress-induced cardiomyopathy, Gebrochenes-Herz syndrome, and stress cardiomyopathy. The recognized effects on the heart include congestive heart failure due to a profound weakening of the myocardium not related to lack of oxygen. This may lead to acute heart failure, lethal arrhythmias, or even the rupture of a ventricle. The exact etiology is not known, but several factors have been suggested, including transient vasospasm, dysfunction of the cardiac capillaries, or thickening of the myocardium—particularly in the left ventricle—that may lead to the critical circulation of blood to this region. While many patients survive the initial acute event with treatment to restore normal function, there is a strong correlation with death. Careful statistical analysis by the Cass Business School, a prestigious institution located in London, published in 2008, revealed that within one year of the death of a loved one, women are more than twice as likely to die and males are six times as likely to die as would otherwise be expected.

Other Factors Influencing Heart Rate

Using a combination of autorhythmicity and innervation, the cardiovascular center is able to provide relatively precise control over HR. However, there are a number of other factors that have an impact on HR as well, including epinephrine, NE, and thyroid hormones; levels of various ions including calcium, potassium, and sodium; body temperature; hypoxia; and pH balance ([link] and [link]). After reading this section, the importance of maintaining homeostasis should become even more apparent.

Major Factors Increasing Heart Rate and Force of Contraction		
Factor	Effect	
Cardioaccelerator nerves	Release of norepinephrine	
Proprioreceptors	Increased rates of firing during exercise	
Chemoreceptors	Decreased levels of O_2 ; increased levels of H^+ , CO_2 , and lactic acid	
Baroreceptors	Decreased rates of firing, indicating falling blood volume/pressure	
Limbic system	Anticipation of physical exercise or strong emotions	
Catecholamines	Increased epinephrine and norepinephrine	
Thyroid hormones	Increased T_3 and T_4	

Major Factors Increasing Heart Rate and Force of Contraction		
Factor	Effect	
Calcium	Increased Ca ²⁺	
Potassium	Decreased K ⁺	
Sodium	Decreased Na ⁺	
Body temperature	Increased body temperature	
Nicotine and caffeine	Stimulants, increasing heart rate	

Factors Decreasing Heart Rate and Force of Contraction		
Factor	Effect	
Cardioinhibitor nerves (vagus)	Release of acetylcholine	
Proprioreceptors	Decreased rates of firing following exercise	
Chemoreceptors	Increased levels of O_2 ; decreased levels of H^+ and CO_2	
Baroreceptors	Increased rates of firing, indicating higher blood volume/pressure	

Factors Decreasing Heart Rate and Force of Contraction		
Factor	Effect	
Limbic system	Anticipation of relaxation	
Catecholamines	Decreased epinephrine and norepinephrine	
Thyroid hormones	Decreased T_3 and T_4	
Calcium	Decreased Ca ²⁺	
Potassium	Increased K ⁺	
Sodium	Increased Na ⁺	
Body temperature	Decrease in body temperature	

Epinephrine and Norepinephrine

The catecholamines, epinephrine and NE, secreted by the adrenal medulla form one component of the extended fight-or-flight mechanism. The other component is sympathetic stimulation. Epinephrine and NE have similar effects: binding to the beta-1 receptors, and opening sodium and calcium ion chemical- or ligand-gated channels. The rate of depolarization is increased by this additional influx of positively charged ions, so the threshold is reached more quickly and the period of repolarization is shortened. However, massive releases of these hormones coupled with sympathetic stimulation may actually lead to arrhythmias. There is no parasympathetic stimulation to the adrenal medulla.

Thyroid Hormones

In general, increased levels of thyroid hormone, or thyroxin, increase cardiac rate and contractility. The impact of thyroid hormone is typically of a much longer duration than that of the catecholamines. The physiologically active form of thyroid hormone, T_3 or triiodothyronine, has been shown to directly enter cardiomyocytes and alter activity at the level of the genome. It also impacts the beta adrenergic response similar to epinephrine and NE described above. Excessive levels of thyroxin may trigger tachycardia.

Caffeine and Nicotine

Caffeine and nicotine are not found naturally within the body. Both of these nonregulated drugs have an excitatory effect on membranes of neurons in general and have a stimulatory effect on the cardiac centers specifically, causing an increase in HR. Caffeine works by increasing the rates of depolarization at the SA node, whereas nicotine stimulates the activity of the sympathetic neurons that deliver impulses to the heart.

Although it is the world's most widely consumed psychoactive drug, caffeine is legal and not regulated. While precise quantities have not been established, "normal" consumption is not considered harmful to most people, although it may cause disruptions to sleep and acts as a diuretic. Its consumption by pregnant women is cautioned against, although no evidence of negative effects has been confirmed. Tolerance and even physical and mental addiction to the drug result in individuals who routinely consume the substance.

Nicotine, too, is a stimulant and produces addiction. While legal and nonregulated, concerns about nicotine's safety and documented links to respiratory and cardiac disease have resulted in warning labels on cigarette packages.

Factors Decreasing Heart Rate

HR can be slowed when a person experiences altered sodium and potassium levels, hypoxia, acidosis, alkalosis, and hypothermia (see [link]). The relationship between electrolytes and HR is complex, but maintaining electrolyte balance is critical to the normal wave of depolarization. Of the two ions, potassium has the greater clinical significance. Initially, both hyponatremia (low sodium levels) and hypernatremia (high sodium levels) may lead to tachycardia. Severely high hypernatremia may lead to fibrillation, which may cause CO to cease. Severe hyponatremia leads to both bradycardia and other arrhythmias. Hypokalemia (low potassium levels) also leads to arrhythmias, whereas hyperkalemia (high potassium levels) causes the heart to become weak and flaccid, and ultimately to fail.

Heart muscle relies exclusively on aerobic metabolism for energy. Hypoxia (an insufficient supply of oxygen) leads to decreasing HRs, since metabolic reactions fueling heart contraction are restricted.

Acidosis is a condition in which excess hydrogen ions are present, and the patient's blood expresses a low pH value. Alkalosis is a condition in which there are too few hydrogen ions, and the patient's blood has an elevated pH. Normal blood pH falls in the range of 7.35–7.45, so a number lower than this range represents acidosis and a higher number represents alkalosis. Recall that enzymes are the regulators or catalysts of virtually all biochemical reactions; they are sensitive to pH and will change shape slightly with values outside their normal range. These variations in pH and accompanying slight physical changes to the active site on the enzyme decrease the rate of formation of the enzyme-substrate complex, subsequently decreasing the rate of many enzymatic reactions, which can have complex effects on HR. Severe changes in pH will lead to denaturation of the enzyme.

The last variable is body temperature. Elevated body temperature is called hyperthermia, and suppressed body temperature is called hypothermia. Slight hyperthermia results in increasing HR and strength of contraction. Hypothermia slows the rate and strength of heart contractions. This distinct slowing of the heart is one component of the larger diving reflex that diverts blood to essential organs while submerged. If sufficiently chilled, the heart will stop beating, a technique that may be employed during open heart

surgery. In this case, the patient's blood is normally diverted to an artificial heart-lung machine to maintain the body's blood supply and gas exchange until the surgery is complete, and sinus rhythm can be restored. Excessive hyperthermia and hypothermia will both result in death, as enzymes drive the body systems to cease normal function, beginning with the central nervous system.

Stroke Volume

Many of the same factors that regulate HR also impact cardiac function by altering SV. While a number of variables are involved, SV is ultimately dependent upon the difference between EDV and ESV. The three primary factors to consider are preload, or the stretch on the ventricles prior to contraction; the contractility, or the force or strength of the contraction itself; and afterload, the force the ventricles must generate to pump blood against the resistance in the vessels. These factors are summarized in [link] and [link].

Preload

Preload is another way of expressing EDV. Therefore, the greater the EDV is, the greater the preload is. One of the primary factors to consider is **filling time**, or the duration of ventricular diastole during which filling occurs. The more rapidly the heart contracts, the shorter the filling time becomes, and the lower the EDV and preload are. This effect can be partially overcome by increasing the second variable, contractility, and raising SV, but over time, the heart is unable to compensate for decreased filling time, and preload also decreases.

With increasing ventricular filling, both EDV or preload increase, and the cardiac muscle itself is stretched to a greater degree. At rest, there is little stretch of the ventricular muscle, and the sarcomeres remain short. With increased ventricular filling, the ventricular muscle is increasingly stretched and the sarcomere length increases. As the sarcomeres reach their optimal lengths, they will contract more powerfully, because more of the myosin

heads can bind to the actin on the thin filaments, forming cross bridges and increasing the strength of contraction and SV. If this process were to continue and the sarcomeres stretched beyond their optimal lengths, the force of contraction would decrease. However, due to the physical constraints of the location of the heart, this excessive stretch is not a concern.

The relationship between ventricular stretch and contraction has been stated in the well-known **Frank-Starling mechanism** or simply Starling's Law of the Heart. This principle states that, within physiological limits, the force of heart contraction is directly proportional to the initial length of the muscle fiber. This means that the greater the stretch of the ventricular muscle (within limits), the more powerful the contraction is, which in turn increases SV. Therefore, by increasing preload, you increase the second variable, contractility.

Otto Frank (1865–1944) was a German physiologist; among his many published works are detailed studies of this important heart relationship. Ernest Starling (1866–1927) was an important English physiologist who also studied the heart. Although they worked largely independently, their combined efforts and similar conclusions have been recognized in the name "Frank-Starling mechanism."

Any sympathetic stimulation to the venous system will increase venous return to the heart, which contributes to ventricular filling, and EDV and preload. While much of the ventricular filling occurs while both atria and ventricles are in diastole, the contraction of the atria, the atrial kick, plays a crucial role by providing the last 20–30 percent of ventricular filling.

Contractility

It is virtually impossible to consider preload or ESV without including an early mention of the concept of contractility. Indeed, the two parameters are intimately linked. Contractility refers to the force of the contraction of the heart muscle, which controls SV, and is the primary parameter for impacting ESV. The more forceful the contraction is, the greater the SV and

smaller the ESV are. Less forceful contractions result in smaller SVs and larger ESVs. Factors that increase contractility are described as **positive inotropic factors**, and those that decrease contractility are described as **negative inotropic factors** (ino- = "fiber;" -tropic = "turning toward").

Not surprisingly, sympathetic stimulation is a positive inotrope, whereas parasympathetic stimulation is a negative inotrope. Sympathetic stimulation triggers the release of NE at the neuromuscular junction from the cardiac nerves and also stimulates the adrenal cortex to secrete epinephrine and NE. In addition to their stimulatory effects on HR, they also bind to both alpha and beta receptors on the cardiac muscle cell membrane to increase metabolic rate and the force of contraction. This combination of actions has the net effect of increasing SV and leaving a smaller residual ESV in the ventricles. In comparison, parasympathetic stimulation releases ACh at the neuromuscular junction from the vagus nerve. The membrane hyperpolarizes and inhibits contraction to decrease the strength of contraction and SV, and to raise ESV. Since parasympathetic fibers are more widespread in the atria than in the ventricles, the primary site of action is in the upper chambers. Parasympathetic stimulation in the atria decreases the atrial kick and reduces EDV, which decreases ventricular stretch and preload, thereby further limiting the force of ventricular contraction. Stronger parasympathetic stimulation also directly decreases the force of contraction of the ventricles.

Several synthetic drugs, including dopamine and isoproterenol, have been developed that mimic the effects of epinephrine and NE by stimulating the influx of calcium ions from the extracellular fluid. Higher concentrations of intracellular calcium ions increase the strength of contraction. Excess calcium (hypercalcemia) also acts as a positive inotropic agent. The drug digitalis lowers HR and increases the strength of the contraction, acting as a positive inotropic agent by blocking the sequestering of calcium ions into the sarcoplasmic reticulum. This leads to higher intracellular calcium levels and greater strength of contraction. In addition to the catecholamines from the adrenal medulla, other hormones also demonstrate positive inotropic effects. These include thyroid hormones and glucagon from the pancreas.

Negative inotropic agents include hypoxia, acidosis, hyperkalemia, and a variety of synthetic drugs. These include numerous beta blockers and calcium channel blockers. Early beta blocker drugs include propranolol and pronethalol, and are credited with revolutionizing treatment of cardiac patients experiencing angina pectoris. There is also a large class of dihydropyridine, phenylalkylamine, and benzothiazepine calcium channel blockers that may be administered decreasing the strength of contraction and SV.

Afterload

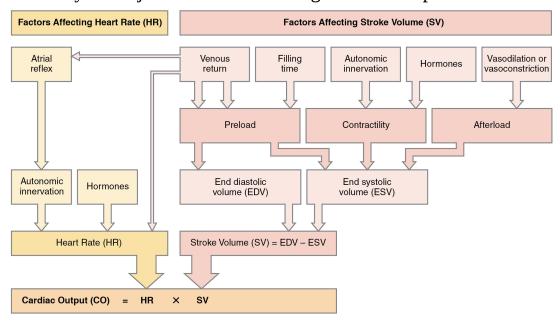
Afterload refers to the tension that the ventricles must develop to pump blood effectively against the resistance in the vascular system. Any condition that increases resistance requires a greater afterload to force open the semilunar valves and pump the blood. Damage to the valves, such as stenosis, which makes them harder to open will also increase afterload. Any decrease in resistance decreases the afterload. [link] summarizes the major factors influencing SV, [link] summarizes the major factors influencing CO, and [link] and [link] summarize cardiac responses to increased and decreased blood flow and pressure in order to restore homeostasis.

Major Factors Influencing Stroke Volume

	F	Factors Affecting Stroke Volume (SV)	
	Preload	Contractility	Afterload
Raised due to:	fast filling time increased venous return	sympathetic stimulation epinephrine and norepinephrine high intracellular calcium ions high blood calcium level thyroid hormones glucagon	increased vascular restistance semilunar valve damage
	Increases end diastolic volume, Increases stroke volume	Decreases end systolic volume, Increases stroke volume	Increases end systolic volume Decreases stroke volume
Lowered due to:	decreased thyroid hormones decreased calcium ions high or low potassium ions high or low sodium low body temperature hypoxia abnormal pH balance drugs (i.e., calcium channel blockers)	parasympathetic stimulation acetylcholine hypoxia hyperkalemia	decreased vascular resistance
	Decreases end diastolic volume, Decreases stroke volume	Increases end systolic volume Decreases stroke volume	Decreases end systolic volume Increases stroke volume

Multiple factors impact preload, afterload, and contractility, and are the major considerations influencing SV.

Summary of Major Factors Influencing Cardiac Output



The primary factors influencing HR include autonomic innervation plus endocrine control. Not shown are environmental factors, such as electrolytes, metabolic products, and temperature. The primary factors controlling SV include preload, contractility, and afterload. Other factors such as electrolytes may be classified as either positive or negative inotropic agents.

Cardiac Response to Decreasing Blood Flow and Pressure Due to Decreasing Cardiac Output

	sponse to Decreasing Blood I CaBdiace@epports (aorta, carotid arteries, venae cavae, and atria) Baroreceptors (aorta, carotid arteries, venae	Flo@landdreceptor D(both central nervous system and in proximity to barefree Episors (both central nervous system and in proximity to
	cavae, and atria)	baroreceptors)
Sensitive to	Decreasing stretch	Decreasing O_2 and increasing CO_2 , H^+ , and lactic acid
Target	Parasympathetic stimulation suppressed	Sympathetic stimulation increased
Response of heart	Increasing heart rate and increasing stroke volume	Increasing heart rate and increasing stroke volume
Overall effect	Increasing blood flow and pressure due to increasing cardiac output; hemostasis restored	Increasing blood flow and pressure due to increasing cardiac output; hemostasis restored

Cardiac Response to Increasing Blood Flow and Pressure Due to Increasing Cardiac Output

	Baroreceptors (aorta, carotid arteries, venae cavae, and atria)	Chemoreceptors (both central nervous system and in proximity to baroreceptors)
Sensitive to	Increasing stretch	Increasing O_2 and decreasing CO_2 , H^+ , and lactic acid
Target	Parasympathetic stimulation increased	Sympathetic stimulation suppressed
Response of heart	Decreasing heart rate and decreasing stroke volume	Decreasing heart rate and decreasing stroke volume
Overall effect	Decreasing blood flow and pressure due to decreasing cardiac output; hemostasis restored	Decreasing blood flow and pressure due to decreasing cardiac output; hemostasis restored

Chapter Review

Many factors affect HR and SV, and together, they contribute to cardiac function. HR is largely determined and regulated by autonomic stimulation and hormones. There are several feedback loops that contribute to maintaining homeostasis dependent upon activity levels, such as the atrial reflex, which is determined by venous return.

SV is regulated by autonomic innervation and hormones, but also by filling time and venous return. Venous return is determined by activity of the skeletal muscles, blood volume, and changes in peripheral circulation. Venous return determines preload and the atrial reflex. Filling time directly related to HR also determines preload. Preload then impacts both EDV and ESV. Autonomic innervation and hormones largely regulate contractility.

Contractility impacts EDV as does afterload. CO is the product of HR multiplied by SV. SV is the difference between EDV and ESV.

Glossary

afterload

force the ventricles must develop to effectively pump blood against the resistance in the vessels

autonomic tone

contractile state during resting cardiac activity produced by mild sympathetic and parasympathetic stimulation

atrial reflex

(also, called Bainbridge reflex) autonomic reflex that responds to stretch receptors in the atria that send impulses to the cardioaccelerator area to increase HR when venous flow into the atria increases

baroreceptor reflex

autonomic reflex in which the cardiac centers monitor signals from the baroreceptor stretch receptors and regulate heart function based on blood flow

cardiac output (CO)

amount of blood pumped by each ventricle during one minute; equals HR multiplied by SV

cardiac plexus

paired complex network of nerve fibers near the base of the heart that receive sympathetic and parasympathetic stimulations to regulate HR

cardiac reflexes

series of autonomic reflexes that enable the cardiovascular centers to regulate heart function based upon sensory information from a variety of visceral sensors

cardiac reserve

difference between maximum and resting CO

ejection fraction

portion of the blood that is pumped or ejected from the heart with each contraction; mathematically represented by SV divided by EDV

filling time

duration of ventricular diastole during which filling occurs

Frank-Starling mechanism

relationship between ventricular stretch and contraction in which the force of heart contraction is directly proportional to the initial length of the muscle fiber

heart rate (HR)

number of times the heart contracts (beats) per minute

negative inotropic factors

factors that negatively impact or lower heart contractility

positive inotropic factors

factors that positively impact or increase heart contractility

stroke volume (SV)

amount of blood pumped by each ventricle per contraction; also, the difference between EDV and ESV

target heart rate

range in which both the heart and lungs receive the maximum benefit from an aerobic workout

OU Human Physiology: Blood Vessels and Blood Introduction class="introduction" Blood Vessels

While most blood vessels are located deep from the surface and are not visible, the superficial veins of the upper limb provide an indication of the extent, prominence , and importance of these structures to the body. (credit: Colin Davis)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Compare and contrast the anatomical structure and function of arteries, arterioles, capillaries, venules, and veins
- Accurately describe the forces that account for capillary exchange
- List the major factors affecting blood flow, blood pressure, and resistance
- Use a sphygmomanometer to take a manual blood pressure
- Describe how blood flow, blood pressure, and resistance interrelate
- Discuss how the neural and endocrine mechanisms maintain homeostasis within the blood vessels
- Describe the interaction of the cardiovascular system with other body systems
- Discuss the common disorders that affect vascular homeostasis

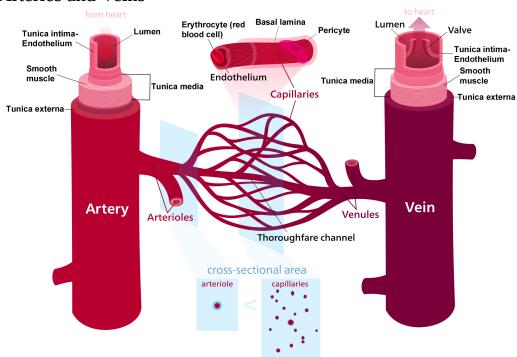
In this chapter, you will learn about the vascular part of the cardiovascular system, that is, the vessels that transport blood throughout the body and provide the physical site where gases, nutrients, and other substances are exchanged with body cells. When vessel functioning is reduced, bloodborne substances do not circulate effectively throughout the body. As a result, tissue injury occurs, metabolism is impaired, and the functions of every bodily system are threatened.

OU Human Physiology: Structure and Function of Blood Vessels By the end of this section, you will be able to:

- Compare and contrast the anatomical structure and function of arteries, arterioles, capillaries, venules, and veins
- List the vessels that are innervated by sympathetic fibers of the autonomic nervous system and the location for this innervation
- Describe the purpose of vasoconstriction and vasodilation of arterioles and veins

Blood is carried through the body via blood vessels. An artery is a blood vessel that carries blood away from the heart, where it branches into eversmaller vessels. Eventually, the smallest arteries, vessels called arterioles, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart ([link]).

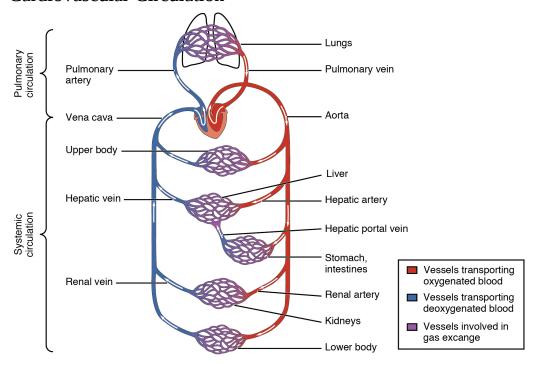
Arteries and Veins



Arteries and veins are comprised of many layers and are connected through capillaries.

Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit ([link]). Systemic arteries provide blood rich in oxygen to the body's tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has been delivered to the cells. In contrast, in the pulmonary circuit, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.

Cardiovascular Circulation

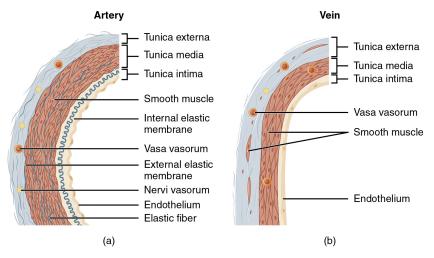


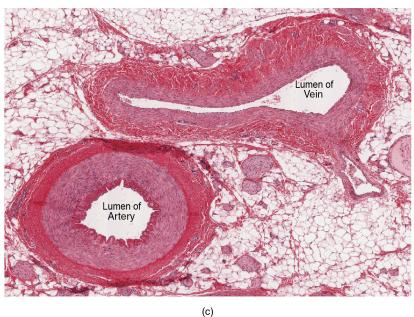
The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.

Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. Arteries and arterioles have thicker walls than veins and venules because they are closer to the heart and receive blood that is surging at a far greater pressure ([link]). Each type of vessel has a lumen—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls and smaller diameters give arterial lumens a more rounded appearance in cross section than the lumens of veins.

Structure of Blood Vessels





(a) Arteries and (b) veins share the same general features, but the walls of arteries are much thicker because of the higher pressure of the blood that flows through them. (c) A micrograph shows the relative differences in thickness. LM × 160. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

By the time blood has passed through capillaries and entered venules, the pressure initially exerted upon it by heart contractions has diminished. In other words, in comparison to arteries, venules and veins withstand a much lower pressure from the blood that flows through them. Their walls are considerably thinner and their lumens are correspondingly larger in diameter, allowing more blood to flow with less vessel resistance. In addition, many veins of the body, particularly those of the limbs, contain valves that assist the unidirectional flow of blood toward the heart. This is critical because blood flow becomes sluggish in the extremities, as a result of the lower pressure and the effects of gravity.

The walls of arteries and veins are largely composed of living cells and their products (including collagenous and elastic fibers); the cells require nourishment and produce waste. Since blood passes through the larger vessels relatively quickly, there is limited opportunity for blood in the lumen of the vessel to provide nourishment to or remove waste from the vessel's cells. Further, the walls of the larger vessels are too thick for nutrients to diffuse through to all of the cells. Larger arteries and veins contain small blood vessels within their walls known as the vasa vasorum literally "vessels of the vessel"—to provide them with this critical exchange. Since the pressure within arteries is relatively high, the vasa vasorum must function in the outer layers of the vessel (see [link]) or the pressure exerted by the blood passing through the vessel would collapse it, preventing any exchange from occurring. The lower pressure within veins allows the vasa vasorum to be located closer to the lumen. The restriction of the vasa vasorum to the outer layers of arteries is thought to be one reason that arterial diseases are more common than venous diseases, since its location makes it more difficult to nourish the cells of the arteries and remove waste products. There are also minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle. These minute nerves are known as the nervi vasorum.

Both arteries and veins have the same three distinct tissue layers, called tunics (from the Latin term tunica), for the garments first worn by ancient Romans; the term tunic is also used for some modern garments. From the most interior layer to the outer, these tunics are the tunica intima, the tunica

media, and the tunica externa (see [link]). [link] compares and contrasts the tunics of the arteries and veins.

Comparison of Tunics in Arteries and Veins		
	Arteries	Veins
General appearance	Thick walls with small lumens Generally appear rounded	Thin walls with large lumens Generally appear flattened
Tunica intima	Endothelium usually appears wavy due to constriction of smooth muscle Internal elastic membrane present in larger vessels	Endothelium appears smooth Internal elastic membrane absent

	son of Tunics in Arteries and Veins Arteries Veins	
Tunica media	Normally the thickest layer in arteries Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart) External elastic membrane present in larger vessels	Normally thinner than the tunica externa Smooth muscle cells and collagenous fibers predominate Nervi vasorum and vasa vasorum present External elastic membrane absent
Tunica externa	Normally thinner than the tunica media in all but the largest arteries Collagenous and elastic fibers Nervi vasorum and vasa vasorum present	Normally the thickest layer in veins Collagenous and smooth fibers predominate Some smooth muscle fibers Nervi vasorum and vasa vasorum present

Tunica Intima

The **tunica intima** (also called the tunica interna) is composed of epithelial and connective tissue layers. Lining the tunica intima is the specialized simple squamous epithelium called the endothelium, which is continuous throughout the entire vascular system, including the lining of the chambers of the heart. Damage to this endothelial lining and exposure of blood to the collagenous fibers beneath is one of the primary causes of clot formation. Until recently, the endothelium was viewed simply as the boundary between the blood in the lumen and the walls of the vessels. Recent studies, however, have shown that it is physiologically critical to such activities as helping to regulate capillary exchange and altering blood flow. The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure. Uncompensated overproduction of endothelins may contribute to hypertension (high blood pressure) and cardiovascular disease.

Next to the endothelium is the basement membrane, or basal lamina, that effectively binds the endothelium to the connective tissue. The basement membrane provides strength while maintaining flexibility, and it is permeable, allowing materials to pass through it. The thin outer layer of the tunica intima contains a small amount of areolar connective tissue that consists primarily of elastic fibers to provide the vessel with additional flexibility; it also contains some collagenous fibers to provide additional strength.

In larger arteries, there is also a thick, distinct layer of elastic fibers known as the internal elastic membrane (also called the internal elastic lamina) at the boundary with the tunica media. Like the other components of the tunica intima, the internal elastic membrane provides structure while allowing the vessel to stretch. It is permeated with small openings that allow exchange of materials between the tunics. The internal elastic membrane is not apparent in veins. In addition, many veins, particularly in the lower limbs, contain valves formed by sections of thickened endothelium that are reinforced with connective tissue, extending into the lumen.

Under the microscope, the lumen and the entire tunica intima of a vein will appear smooth, whereas those of an artery will normally appear wavy because of the partial constriction of the smooth muscle in the tunica media, the next layer of blood vessel walls.

Tunica Media

The **tunica media** is the substantial middle layer of the vessel wall (see [link]). It is generally the thickest layer in arteries, and it is much thicker in arteries than it is in veins. The tunica media consists of layers of smooth muscle supported by connective tissue that is primarily made up of elastic fibers, most of which are arranged in circular sheets. Toward the outer portion of the tunic, there are also layers of longitudinal muscle. Contraction and relaxation of the circular muscles decrease and increase the diameter of the vessel lumen, respectively. Specifically in arteries, vasoconstriction decreases blood flow as the smooth muscle in the walls of the tunica media contracts, making the lumen narrower and increasing blood pressure. Similarly, **vasodilation** increases blood flow as the smooth muscle relaxes, allowing the lumen to widen and blood pressure to drop. Both vasoconstriction and vasodilation are regulated in part by small vascular nerves, known as nervi vasorum, or "nerves of the vessel," that run within the walls of blood vessels. These are generally all sympathetic fibers, although some trigger vasodilation and others induce vasoconstriction, depending upon the nature of the neurotransmitter and receptors located on the target cell. Nervous control over vessels tends to be more generalized than the specific targeting of individual blood vessels. Local controls, discussed later, account for this phenomenon. (Seek additional content for more information on these dynamic aspects of the autonomic nervous system.) Hormones and local chemicals also control blood vessels. Together, these neural and chemical mechanisms reduce or increase blood flow in response to changing body conditions, from exercise to hydration. Regulation of both blood flow and blood pressure is discussed in detail later in this chapter.

The smooth muscle layers of the tunica media are supported by a framework of collagenous fibers that also binds the tunica media to the

inner and outer tunics. Along with the collagenous fibers are large numbers of elastic fibers that appear as wavy lines in prepared slides. Separating the tunica media from the outer tunica externa in larger arteries is the external elastic membrane (also called the external elastic lamina), which also appears wavy in slides. This structure is not usually seen in smaller arteries, nor is it seen in veins.

Tunica Externa

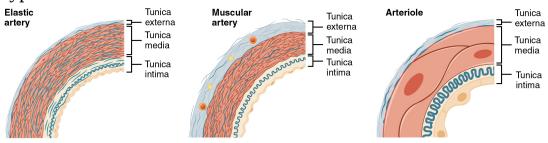
The outer tunic, the **tunica externa** (also called the tunica adventitia), is a substantial sheath of connective tissue composed primarily of collagenous fibers. Some bands of elastic fibers are found here as well. The tunica externa in veins also contains groups of smooth muscle fibers. This is normally the thickest tunic in veins and may be thicker than the tunica media in some larger arteries. The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position. If you are able to palpate some of the superficial veins on your upper limbs and try to move them, you will find that the tunica externa prevents this. If the tunica externa did not hold the vessel in place, any movement would likely result in disruption of blood flow.

Arteries

An **artery** is a blood vessel that conducts blood away from the heart. All arteries have relatively thick walls that can withstand the high pressure of blood ejected from the heart. However, those close to the heart have the thickest walls, containing a high percentage of elastic fibers in all three of their tunics. This type of artery is known as an **elastic artery** ([link]). Vessels larger than 10 mm in diameter are typically elastic. Their abundant elastic fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to recoil after the surge has passed. If artery walls were rigid and unable to expand and recoil, their resistance to blood flow would greatly increase and blood pressure would rise to even higher levels, which would in turn require the heart to pump harder to increase the

volume of blood expelled by each pump (the stroke volume) and maintain adequate pressure and flow. Artery walls would have to become even thicker in response to this increased pressure. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.

Types of Arteries and Arterioles



Comparison of the walls of an elastic artery, a muscular artery, and an arteriole is shown. In terms of scale, the diameter of an arteriole is measured in micrometers compared to millimeters for elastic and muscular arteries.

Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery's tunica intima decreases and the amount of smooth muscle in its tunica media increases. The artery at this point is described as a **muscular artery**. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in vasoconstriction. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no "line of demarcation" where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the vascular tree repeatedly branches. In turn, muscular arteries branch to

distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

Arterioles

An **arteriole** is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin (see [link]).

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as resistance vessels. The muscle fibers in arterioles are normally slightly contracted, causing arterioles to maintain a consistent muscle tone—in this case referred to as vascular tone—in a similar manner to the muscular tone of skeletal muscle. In reality, all blood vessels exhibit vascular tone due to the partial contraction of smooth muscle. The importance of the arterioles is that they will be the primary site of both resistance and regulation of blood pressure. The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls, and vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

Capillaries

A **capillary** is a microscopic channel that supplies blood to the tissues themselves, a process called **perfusion**. Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through. Flow through capillaries is often described as **microcirculation**.

The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth muscle fibers. There is some

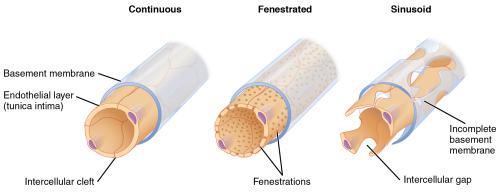
variation in wall structure: In a large capillary, several endothelial cells bordering each other may line the lumen; in a small capillary, there may be only a single cell layer that wraps around to contact itself.

For capillaries to function, their walls must be leaky, allowing substances to pass through. There are three major types of capillaries, which differ according to their degree of "leakiness:" continuous, fenestrated, and sinusoid capillaries ([link]).

Continuous Capillaries

The most common type of capillary, the **continuous capillary**, is found in almost all vascularized tissues. Continuous capillaries are characterized by a complete endothelial lining with tight junctions between endothelial cells. Although a tight junction is usually impermeable and only allows for the passage of water and ions, they are often incomplete in capillaries, leaving intercellular clefts that allow for exchange of water and other very small molecules between the blood plasma and the interstitial fluid. Substances that can pass between cells include metabolic products, such as glucose, water, and small hydrophobic molecules like gases and hormones, as well as various leukocytes. Continuous capillaries not associated with the brain are rich in transport vesicles, contributing to either endocytosis or exocytosis. Those in the brain are part of the blood-brain barrier. Here, there are tight junctions and no intercellular clefts, plus a thick basement membrane and astrocyte extensions called end feet; these structures combine to prevent the movement of nearly all substances.

Types of Capillaries



The three major types of capillaries: continuous, fenestrated, and sinusoid.

Fenestrated Capillaries

A **fenestrated capillary** is one that has pores (or fenestrations) in addition to tight junctions in the endothelial lining. These make the capillary permeable to larger molecules. The number of fenestrations and their degree of permeability vary, however, according to their location. Fenestrated capillaries are common in the small intestine, which is the primary site of nutrient absorption, as well as in the kidneys, which filter the blood. They are also found in the choroid plexus of the brain and many endocrine structures, including the hypothalamus, pituitary, pineal, and thyroid glands.

Sinusoid Capillaries

A sinusoid capillary (or discontinuous) is the least common type of capillary. Sinusoid capillaries are flattened, and they have extensive intercellular gaps and incomplete basement membranes, in addition to intercellular clefts and fenestrations. This gives them an appearance not unlike Swiss cheese. These very large openings allow for the passage of the largest molecules, including plasma proteins and even cells. Blood flow through sinusoids is very slow, allowing more time for exchange of gases, nutrients, and wastes. Sinusoids are found in the liver and spleen, bone marrow, lymph nodes (where they carry lymph, not blood), and many endocrine glands including the pituitary and adrenal glands. Without these specialized capillaries, these organs would not be able to provide their myriad of functions. For example, when bone marrow forms new blood cells, the cells must enter the blood supply and can only do so through the large openings of a sinusoid capillary; they cannot pass through the small openings of continuous or fenestrated capillaries. The liver also requires

extensive specialized sinusoid capillaries in order to process the materials brought to it by the hepatic portal vein from both the digestive tract and spleen, and to release plasma proteins into circulation.

Note:



Go watch this <u>video</u> to learn more about the different types of capillaries.

Metarterioles and Capillary Beds

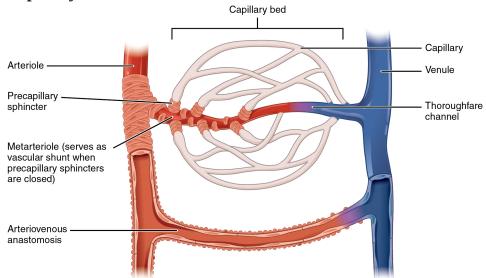
A **metarteriole** is a type of vessel that has structural characteristics of both an arteriole and a capillary. Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries. Each metarteriole arises from a terminal arteriole and branches to supply blood to a **capillary bed** that may consist of 10–100 capillaries.

The **precapillary sphincters**, circular smooth muscle cells that surround the capillary at its origin with the metarteriole, tightly regulate the flow of blood from a metarteriole to the capillaries it supplies. Their function is critical: If all of the capillary beds in the body were to open simultaneously, they would collectively hold every drop of blood in the body and there would be none in the arteries, arterioles, venules, veins, or the heart itself. Normally, the precapillary sphincters are closed. When the surrounding tissues need oxygen and have excess waste products, the precapillary sphincters open, allowing blood to flow through and exchange to occur before closing once more ([link]). If all of the precapillary sphincters in a

capillary bed are closed, blood will flow from the metarteriole directly into a **thoroughfare channel** and then into the venous circulation, bypassing the capillary bed entirely. This creates what is known as a **vascular shunt**.

Although you might expect blood flow through a capillary bed to be smooth, in reality, it moves with an irregular, pulsating flow. This pattern is called vasomotion and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels. For example, during strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open, as they would be in the digestive system when nutrients are present in the digestive tract. During sleep or rest periods, vessels in both areas are largely closed; they open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.

Capillary Bed



In a capillary bed, arterioles give rise to metarterioles. Precapillary sphincters located at the junction of a metarteriole with a capillary regulate blood flow. A thoroughfare channel connects the metarteriole to a venule. An arteriovenous anastomosis, which directly connects the arteriole with the venule, is shown at the bottom.

Note:



Go watch this <u>video</u> to learn more about precapillary sphinters.

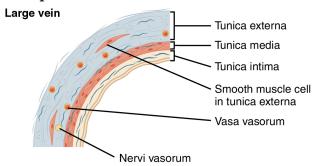
Venules

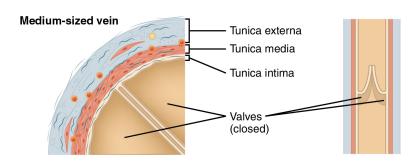
A **venule** is an extremely small vein, generally 8–100 micrometers in diameter. Postcapillary venules join multiple capillaries exiting from a capillary bed. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa ([link]). Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

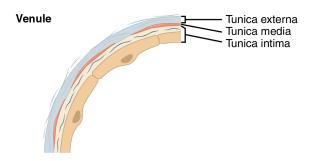
Veins

A **vein** is a blood vessel that conducts blood toward the heart. Compared to arteries, veins are thin-walled vessels with large and irregular lumens (see [link]). Because they are low-pressure vessels, larger veins are commonly equipped with valves that promote the unidirectional flow of blood toward the heart and prevent backflow toward the capillaries caused by the inherent low blood pressure in veins as well as the pull of gravity. [link] compares the features of arteries and veins.

Comparison of Veins and Venules







Many veins have valves to prevent back flow of blood, whereas venules do not. In terms of scale, the diameter of a venule is measured in micrometers compared to millimeters for veins.

Comparison of Arteries and Veins		
	Arteries	Veins
Direction of blood flow	Conducts blood away from the heart	Conducts blood toward the heart
General appearance	Rounded	Irregular, often collapsed
Pressure	High	Low
Wall thickness	Thick	Thin
Relative oxygen concentration	Higher in systemic arteries Lower in pulmonary arteries	Lower in systemic veins Higher in pulmonary veins
Valves	Not present	Present most commonly in limbs and in veins inferior to the heart

Note:

Disorders of the...

Cardiovascular System: Edema and Varicose Veins

Despite the presence of valves and the contributions of other anatomical and physiological adaptations we will cover shortly, over the course of a day, some blood will inevitably pool, especially in the lower limbs, due to the pull of gravity. Any blood that accumulates in a vein will increase the

pressure within it, which can then be reflected back into the smaller veins, venules, and eventually even the capillaries. Increased pressure will promote the flow of fluids out of the capillaries and into the interstitial fluid. The presence of excess tissue fluid around the cells leads to a condition called edema.

Most people experience a daily accumulation of tissue fluid, especially if they spend much of their work life on their feet (like most health professionals). However, clinical edema goes beyond normal swelling and requires medical treatment. Edema has many potential causes, including hypertension and heart failure, severe protein deficiency, renal failure, and many others. In order to treat edema, which is a sign rather than a discrete disorder, the underlying cause must be diagnosed and alleviated.

Varicose Veins



Varicose veins are commonly found in the lower limbs. (credit: Thomas Kriese)

Edema may be accompanied by varicose veins, especially in the superficial veins of the legs ([link]). This disorder arises when defective valves allow blood to accumulate within the veins, causing them to distend, twist, and become visible on the surface of the integument. Varicose veins may occur in both sexes, but are more common in women and are often related to pregnancy. More than simple cosmetic blemishes, varicose veins are often painful and sometimes itchy or throbbing. Without treatment, they tend to grow worse over time. The use of support hose, as well as elevating the feet and legs whenever possible, may be helpful in alleviating this condition. Laser surgery and interventional radiologic procedures can reduce the size and severity of varicose veins. Severe cases may require conventional surgery to remove the damaged vessels. As there are typically redundant circulation patterns, that is, anastomoses, for the smaller and more superficial veins, removal does not typically impair the circulation. There is evidence that patients with varicose veins suffer a greater risk of developing a thrombus or clot.

Veins as Blood Reservoirs

In addition to their primary function of returning blood to the heart, veins may be considered blood reservoirs, since systemic veins contain approximately 64 percent of the blood volume at any given time ([link]). Their ability to hold this much blood is due to their high **capacitance**, that is, their capacity to distend (expand) readily to store a high volume of blood, even at a low pressure. The large lumens and relatively thin walls of veins make them far more distensible than arteries; thus, they are said to be **capacitance vessels**.

Distribution of Blood Flow

Systemic circulation 84%	Systemic veins 64%	Large veins 18%		
		Large venous networks (liver, bone marrow, and integument) 21%		
		Venules and medium-sized veins 25%		
	Systemic arteries 13%	Arterioles 2%		
		Muscular arteries 5%		
		Elastic arteries 4%		
		Aorta 2%		
	Systemic capillaries 7%	Systemic capillaries 7%		
Pulmonary circulation 9%	Pulmonary veins 4%			
	Pulmonary capillaries 2%			
	Pulmonary arteries 3%			
Heart 7%				

When blood flow needs to be redistributed to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction—or in this case, venoconstriction. Less dramatic than the vasoconstriction seen in smaller arteries and arterioles, venoconstriction may be likened to a "stiffening" of the vessel wall. This increases pressure on the blood within the veins, speeding its return to the heart. As you will note in [link], approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as **venous reserve**. Through venoconstriction, this "reserve" volume of blood can get back to the heart more quickly for redistribution to other parts of the circulation.

Note:

Career Connection

Vascular Surgeons and Technicians

Vascular surgery is a specialty in which the physician deals primarily with diseases of the vascular portion of the cardiovascular system. This includes repair and replacement of diseased or damaged vessels, removal of plaque from vessels, minimally invasive procedures including the insertion of venous catheters, and traditional surgery. Following completion of medical school, the physician generally completes a 5-year surgical residency followed by an additional 1 to 2 years of vascular specialty training. In the United States, most vascular surgeons are members of the Society of Vascular Surgery.

Vascular technicians are specialists in imaging technologies that provide information on the health of the vascular system. They may also assist physicians in treating disorders involving the arteries and veins. This profession often overlaps with cardiovascular technology, which would also include treatments involving the heart. Although recognized by the American Medical Association, there are currently no licensing requirements for vascular technicians, and licensing is voluntary. Vascular technicians typically have an Associate's degree or certificate, involving 18 months to 2 years of training. The United States Bureau of Labor projects this profession to grow by 29 percent from 2010 to 2020.

Note:



Visit this <u>site</u> to learn more about vascular surgery.

Note:					



Visit this <u>site</u> to learn more about vascular technicians.

Note:



Go watch this <u>video</u> to learn more about the different layers of blood vessels.

Note:



Go watch this <u>video</u> to learn more about the differences between arteries and veins.

Chapter Review

Blood pumped by the heart flows through a series of vessels known as arteries, arterioles, capillaries, venules, and veins before returning to the heart. Arteries transport blood away from the heart and branch into smaller vessels, forming arterioles. Arterioles distribute blood to capillary beds, the sites of exchange with the body tissues. Capillaries lead back to small vessels known as venules that flow into the larger veins and eventually back to the heart.

The arterial system is a relatively high-pressure system, so arteries have thick walls that appear round in cross section. The venous system is a lower-pressure system, containing veins that have larger lumens and thinner walls. They often appear flattened. Arteries, arterioles, venules, and veins are composed of three tunics known as the tunica intima, tunica media, and tunica externa. Capillaries have only a tunica intima layer. The tunica intima is a thin layer composed of a simple squamous epithelium known as endothelium and a small amount of connective tissue. The tunica media is a thicker area composed of variable amounts of smooth muscle and connective tissue. It is the thickest layer in all but the largest arteries. The tunica externa is primarily a layer of connective tissue, although in veins, it also contains some smooth muscle. Blood flow through vessels can be dramatically influenced by vasoconstriction and vasodilation in their walls.

Glossary

arteriole

(also, resistance vessel) very small artery that leads to a capillary

artery

blood vessel that conducts blood away from the heart; may be a conducting or distributing vessel

capacitance ability of a vein to distend and store blood

capacitance vessels veins

capillary

smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

capillary bed

network of 10–100 capillaries connecting arterioles to venules

continuous capillary

most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

elastic artery

(also, conducting artery) artery with abundant elastic fibers located closer to the heart, which maintains the pressure gradient and conducts blood to smaller branches

fenestrated capillary

type of capillary with pores or fenestrations in the endothelium that allow for rapid passage of certain small materials

lumen

interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

metarteriole

short vessel arising from a terminal arteriole that branches to supply a capillary bed

microcirculation

blood flow through the capillaries

muscular artery

(also, distributing artery) artery with abundant smooth muscle in the tunica media that branches to distribute blood to the arteriole network

perfusion

distribution of blood into the capillaries so the tissues can be supplied

precapillary sphincters

circular rings of smooth muscle that surround the entrance to a capillary and regulate blood flow into that capillary

sinusoid capillary

rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

thoroughfare channel

continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

tunica externa

(also, tunica adventitia) outermost layer or tunic of a vessel (except capillaries)

tunica intima

(also, tunica interna) innermost lining or tunic of a vessel

tunica media

middle layer or tunic of a vessel (except capillaries)

vascular shunt

continuation of the metarteriole and thoroughfare channel that allows blood to bypass the capillary beds to flow directly from the arterial to the venous circulation

vasoconstriction

constriction of the smooth muscle of a blood vessel, resulting in a decreased vascular diameter

vasodilation

relaxation of the smooth muscle in the wall of a blood vessel, resulting in an increased vascular diameter

vein

blood vessel that conducts blood toward the heart

venous reserve

volume of blood contained within systemic veins in the integument, bone marrow, and liver that can be returned to the heart for circulation, if needed

venule

small vessel leading from the capillaries to veins

OU Human Physiology: Blood Flow, Blood Pressure, and Resistance By the end of this section, you will be able to:

- Distinguish between systolic pressure, diastolic pressure, pulse pressure, and mean arterial pressure
- Interrelate systole and diastole with systolic and diastolic pressures
- Use a sphygmomanometer to take a manual blood pressure and explain the Korotkoff sounds in relation to blood flow, artery diameter, and systolic and diastolic pressures
- Explain the major factors affecting blood flow, blood pressure, and resistance
- Describe how blood flow, blood pressure, and resistance interrelate
- Identify and discuss the five variables affecting arterial blood flow and blood pressure
- Describe how changes in CVP can indirectly affect MAP
- Discuss the four factors that enhance CVP and therefore venous return

Blood flow refers to the movement of blood through a vessel, tissue, or organ, and is usually expressed in terms of volume of blood per unit of time. It is initiated by the contraction of the ventricles of the heart. Ventricular contraction ejects blood into the major arteries, resulting in flow from regions of higher pressure to regions of lower pressure, as blood encounters smaller arteries and arterioles, then capillaries, then the venules and veins of the venous system. This section discusses a number of critical variables that contribute to blood flow throughout the body. It also discusses the factors that impede or slow blood flow, a phenomenon known as **resistance**.

As noted earlier, hydrostatic pressure is the force exerted by a fluid due to gravitational pull, usually against the wall of the container in which it is located. One form of hydrostatic pressure is **blood pressure**, the force exerted by blood upon the walls of the blood vessels or the chambers of the heart. Blood pressure may be measured in capillaries and veins, as well as the vessels of the pulmonary circulation; however, the term blood pressure without any specific descriptors typically refers to systemic arterial blood pressure—that is, the pressure of blood flowing in the arteries of the

systemic circulation. In clinical practice, this pressure is measured in mm Hg and is usually obtained using the brachial artery of the arm.

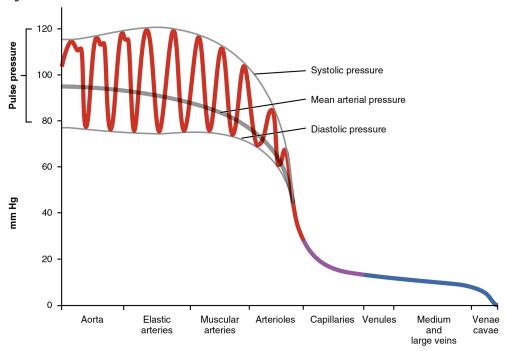
Components of Arterial Blood Pressure

Arterial blood pressure in the larger vessels consists of several distinct components ([link]): systolic and diastolic pressures, pulse pressure, and mean arterial pressure.

Systolic and Diastolic Pressures

When systemic arterial blood pressure is measured, it is recorded as a ratio of two numbers (e.g., 120/80 is a normal adult blood pressure), expressed as systolic pressure over diastolic pressure. The **systolic pressure** is the higher value (typically around 120 mm Hg) and reflects the arterial pressure resulting from the ejection of blood during ventricular contraction, or systole. The **diastolic pressure** is the lower value (usually about 80 mm Hg) and represents the arterial pressure of blood during ventricular relaxation, or diastole.

Systemic Blood Pressure



The graph shows the components of blood pressure throughout the blood vessels, including systolic, diastolic, mean arterial, and pulse pressures.

Pulse Pressure

As shown in [link], the difference between the systolic pressure and the diastolic pressure is the **pulse pressure**. For example, an individual with a systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg would have a pulse pressure of 40 mmHg.

Generally, a pulse pressure should be at least 25 percent of the systolic pressure. A pulse pressure below this level is described as low or narrow. This may occur, for example, in patients with a low stroke volume, which may be seen in congestive heart failure, stenosis of the aortic valve, or significant blood loss following trauma. In contrast, a high or wide pulse pressure is common in healthy people following strenuous exercise, when their resting pulse pressure of 30–40 mm Hg may increase temporarily to 100 mm Hg as stroke volume increases. A persistently high pulse pressure at or above 100 mm Hg may indicate excessive resistance in the arteries and can be caused by a variety of disorders. Chronic high resting pulse pressures can degrade the heart, brain, and kidneys, and warrant medical treatment.

Mean Arterial Pressure

Mean arterial pressure (MAP) represents the "average" pressure of blood in the arteries, that is, the average force driving blood into vessels that serve the tissues. Mean is a statistical concept and is calculated by taking the sum of the values divided by the number of values. Although complicated to measure directly and complicated to calculate, MAP can be approximated

by adding the diastolic pressure to one-third of the pulse pressure or systolic pressure minus the diastolic pressure:

$$MAP = diastolic BP + \frac{(systolic - diastolic BP)}{3}$$

In [link], this value is approximately 80 + (120 – 80) / 3, or 93.33. Normally, the MAP falls within the range of 70–110 mm Hg. If the value falls below 60 mm Hg for an extended time, blood pressure will not be high enough to ensure circulation to and through the tissues, which results in **ischemia**, or insufficient blood flow. A condition called **hypoxia**, inadequate oxygenation of tissues, commonly accompanies ischemia. The term hypoxemia refers to low levels of oxygen in systemic arterial blood. Neurons are especially sensitive to hypoxia and may die or be damaged if blood flow and oxygen supplies are not quickly restored.

Pulse

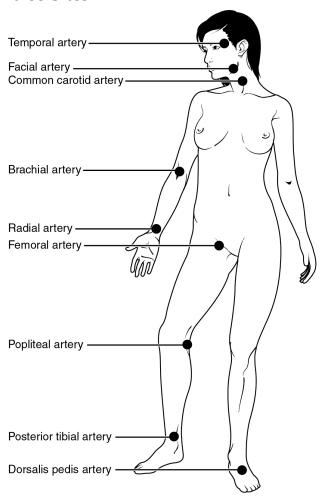
After blood is ejected from the heart, elastic fibers in the arteries help maintain a high-pressure gradient as they expand to accommodate the blood, then recoil. This expansion and recoiling effect, known as the **pulse**, can be palpated manually or measured electronically. Although the effect diminishes over distance from the heart, elements of the systolic and diastolic components of the pulse are still evident down to the level of the arterioles.

Because pulse indicates heart rate, it is measured clinically to provide clues to a patient's state of health. It is recorded as beats per minute. Both the rate and the strength of the pulse are important clinically. A high or irregular pulse rate can be caused by physical activity or other temporary factors, but it may also indicate a heart condition. The pulse strength indicates the strength of ventricular contraction and cardiac output. If the pulse is strong, then systolic pressure is high. If it is weak, systolic pressure has fallen, and medical intervention may be warranted.

Pulse can be palpated manually by placing the tips of the fingers across an artery that runs close to the body surface and pressing lightly. While this

procedure is normally performed using the radial artery in the wrist or the common carotid artery in the neck, any superficial artery that can be palpated may be used ([link]). Common sites to find a pulse include temporal and facial arteries in the head, brachial arteries in the upper arm, femoral arteries in the thigh, popliteal arteries behind the knees, posterior tibial arteries near the medial tarsal regions, and dorsalis pedis arteries in the feet. A variety of commercial electronic devices are also available to measure pulse.

Pulse Sites



The pulse is most readily measured at the radial artery, but can be measured at any of the pulse points shown.

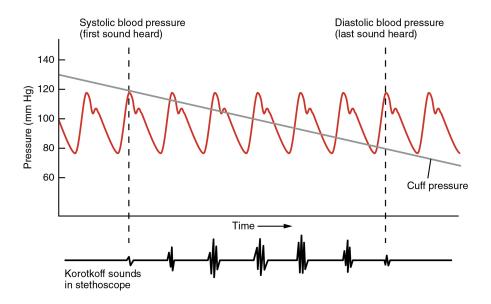
Measurement of Blood Pressure

Blood pressure is one of the critical parameters measured on virtually every patient in every healthcare setting. The technique used today was developed more than 100 years ago by a pioneering Russian physician, Dr. Nikolai Korotkoff. Turbulent blood flow through the vessels can be heard as a soft ticking while measuring blood pressure; these sounds are known as **Korotkoff sounds**. The technique of measuring blood pressure requires the use of a **sphygmomanometer** (a blood pressure cuff attached to a measuring device) and a stethoscope. The technique is as follows:

- The clinician wraps an inflatable cuff tightly around the patient's arm at about the level of the heart.
- The clinician squeezes a rubber pump to inject air into the cuff, raising pressure around the artery and temporarily cutting off blood flow into the patient's arm.
- The clinician places the stethoscope on the patient's antecubital region and, while gradually allowing air within the cuff to escape, listens for the Korotkoff sounds.

Although there are five recognized Korotkoff sounds, only two are normally recorded. Initially, no sounds are heard since there is no blood flow through the vessels, but as air pressure drops, the cuff relaxes, and blood flow returns to the arm. As shown in [link], the first sound heard through the stethoscope—the first Korotkoff sound—indicates systolic pressure. As more air is released from the cuff, blood is able to flow freely through the brachial artery and all sounds disappear. The point at which the last sound is heard is recorded as the patient's diastolic pressure.

Blood Pressure Measurement



When pressure in a sphygmomanometer cuff is released, a clinician can hear the Korotkoff sounds. In this graph, a blood pressure tracing is aligned to a measurement of systolic and diastolic pressures.

The majority of hospitals and clinics have automated equipment for measuring blood pressure that work on the same principles. An even more recent innovation is a small instrument that wraps around a patient's wrist. The patient then holds the wrist over the heart while the device measures blood flow and records pressure.

Note:

Go watch this <u>video</u> to learn more about blood pressure.

Note:



Go watch this <u>video</u> to learn how to take a blood pressure.

Variables Affecting Blood Flow and Blood Pressure

Five variables influence blood flow and blood pressure:

- Cardiac output
- Compliance
- Volume of the blood
- Viscosity of the blood
- Blood vessel length and diameter

Recall that blood moves from higher pressure to lower pressure. It is pumped from the heart into the arteries at high pressure. If you increase pressure in the arteries (afterload), and cardiac function does not compensate, blood flow will actually decrease. In the venous system, the opposite relationship is true. Increased pressure in the veins does not decrease flow as it does in arteries, but actually increases flow. Since pressure in the veins is normally relatively low, for blood to flow back into the heart, the pressure in the atria during atrial diastole must be even lower. It normally approaches zero, except when the atria contract (see [link]).

Cardiac Output

Cardiac output is the measurement of blood flow from the heart through the ventricles, and is usually measured in liters per minute. Any factor that causes cardiac output to increase, by elevating heart rate or stroke volume or both, will elevate blood pressure and promote blood flow. These factors include sympathetic stimulation, the catecholamines epinephrine and norepinephrine, thyroid hormones, and increased calcium ion levels. Conversely, any factor that decreases cardiac output, by decreasing heart rate or stroke volume or both, will decrease arterial pressure and blood flow. These factors include parasympathetic stimulation, elevated or decreased potassium ion levels, decreased calcium levels, anoxia, and acidosis.

Compliance

Compliance is the ability of any compartment to expand to accommodate increased content. A metal pipe, for example, is not compliant, whereas a balloon is. The greater the compliance of an artery, the more effectively it is able to expand to accommodate surges in blood flow without increased resistance or blood pressure. Veins are more compliant than arteries and can expand to hold more blood. When vascular disease causes stiffening of arteries, compliance is reduced and resistance to blood flow is increased. The result is more turbulence, higher pressure within the vessel, and reduced blood flow. This increases the work of the heart.

A Mathematical Approach to Factors Affecting Blood Flow

Jean Louis Marie Poiseuille was a French physician and physiologist who devised a mathematical equation describing blood flow and its relationship to known parameters. The same equation also applies to engineering studies of the flow of fluids. Although understanding the math behind the relationships among the factors affecting blood flow is not necessary to understand blood flow, it can help solidify an understanding of their relationships. Please note that even if the equation looks intimidating,

breaking it down into its components and following the relationships will make these relationships clearer, even if you are weak in math. Focus on the three critical variables: radius (r), vessel length (λ), and viscosity (η).

Poiseuille's equation:

Equation:

Blood flow =
$$\frac{\pi \Delta P r^4}{8\eta\lambda}$$

 π is the Greek letter pi, used to represent the mathematical constant that is the ratio of a circle's circumference to its diameter. It may commonly be represented as 3.14, although the actual number extends to infinity.

 ΔP represents the difference in pressure.

r⁴ is the radius (one-half of the diameter) of the vessel to the fourth power.

 η is the Greek letter eta and represents the viscosity of the blood. λ is the Greek letter lambda and represents the length of a blood vessel.

One of several things this equation allows us to do is calculate the resistance in the vascular system. Normally this value is extremely difficult to measure, but it can be calculated from this known relationship:

Equation:

$$Blood \ flow = \frac{\Delta P}{Resistance}$$

If we rearrange this slightly,

Equation:

$$Resistance = \frac{\Delta P}{Blood \ flow}$$

Then by substituting Pouseille's equation for blood flow:

Equation:

$$Resistance = \frac{8\eta\lambda}{\pi r^4}$$

By examining this equation, you can see that there are only three variables: viscosity, vessel length, and radius, since 8 and π are both constants. The important thing to remember is this: Two of these variables, viscosity and vessel length, will change slowly in the body. Only one of these factors, the radius, can be changed rapidly by vasoconstriction and vasodilation, thus dramatically impacting resistance and flow. Further, small changes in the radius will greatly affect flow, since it is raised to the fourth power in the equation.

We have briefly considered how cardiac output and blood volume impact blood flow and pressure; the next step is to see how the other variables (contraction, vessel length, and viscosity) articulate with Pouseille's equation and what they can teach us about the impact on blood flow.

Note:



Go watch this <u>video</u> to learn about the resistance blood encounters in a blood vessel.

Blood Volume

The relationship between blood volume, blood pressure, and blood flow is intuitively obvious. Water may merely trickle along a creek bed in a dry season, but rush quickly and under great pressure after a heavy rain. Similarly, as blood volume decreases, pressure and flow decrease. As blood volume increases, pressure and flow increase.

Under normal circumstances, blood volume varies little. Low blood volume, called **hypovolemia**, may be caused by bleeding, dehydration, vomiting, severe burns, or some medications used to treat hypertension. It is important to recognize that other regulatory mechanisms in the body are so effective at maintaining blood pressure that an individual may be asymptomatic until 10–20 percent of the blood volume has been lost. Treatment typically includes intravenous fluid replacement.

Hypervolemia, excessive fluid volume, may be caused by retention of water and sodium, as seen in patients with heart failure, liver cirrhosis, some forms of kidney disease, hyperaldosteronism, and some glucocorticoid steroid treatments. Restoring homeostasis in these patients depends upon reversing the condition that triggered the hypervolemia.

Blood Viscosity

Viscosity is the thickness of fluids that affects their ability to flow. Clean water, for example, is less viscous than mud. The viscosity of blood is directly proportional to resistance and inversely proportional to flow; therefore, any condition that causes viscosity to increase will also increase resistance and decrease flow. For example, imagine sipping milk, then a milkshake, through the same size straw. You experience more resistance and therefore less flow from the milkshake. Conversely, any condition that causes viscosity to decrease (such as when the milkshake melts) will decrease resistance and increase flow.

Normally the viscosity of blood does not change over short periods of time. The two primary determinants of blood viscosity are the formed elements and plasma proteins. Since the vast majority of formed elements are erythrocytes, any condition affecting erythropoiesis, such as polycythemia

or anemia, can alter viscosity. Since most plasma proteins are produced by the liver, any condition affecting liver function can also change the viscosity slightly and therefore decrease blood flow. Liver abnormalities include hepatitis, cirrhosis, alcohol damage, and drug toxicities. While leukocytes and platelets are normally a small component of the formed elements, there are some rare conditions in which severe overproduction can impact viscosity as well.

Vessel Length and Diameter

The length of a vessel is directly proportional to its resistance: the longer the vessel, the greater the resistance and the lower the flow. As with blood volume, this makes intuitive sense, since the increased surface area of the vessel will impede the flow of blood. Likewise, if the vessel is shortened, the resistance will decrease and flow will increase.

The length of our blood vessels increases throughout childhood as we grow, of course, but is unchanging in adults under normal physiological circumstances. Further, the distribution of vessels is not the same in all tissues. Adipose tissue does not have an extensive vascular supply. One pound of adipose tissue contains approximately 200 miles of vessels, whereas skeletal muscle contains more than twice that. Overall, vessels decrease in length only during loss of mass or amputation. An individual weighing 150 pounds has approximately 60,000 miles of vessels in the body. Gaining about 10 pounds adds from 2000 to 4000 miles of vessels, depending upon the nature of the gained tissue. One of the great benefits of weight reduction is the reduced stress to the heart, which does not have to overcome the resistance of as many miles of vessels.

In contrast to length, the diameter of blood vessels changes throughout the body, according to the type of vessel, as we discussed earlier. The diameter of any given vessel may also change frequently throughout the day in response to neural and chemical signals that trigger vasodilation and vasoconstriction. The **vascular tone** of the vessel is the contractile state of the smooth muscle and the primary determinant of diameter, and thus of resistance and flow. The effect of vessel diameter on resistance is inverse:

Given the same volume of blood, an increased diameter means there is less blood contacting the vessel wall, thus lower friction and lower resistance, subsequently increasing flow. A decreased diameter means more of the blood contacts the vessel wall, and resistance increases, subsequently decreasing flow.

The influence of lumen diameter on resistance is dramatic: A slight increase or decrease in diameter causes a huge decrease or increase in resistance. This is because resistance is inversely proportional to the radius of the blood vessel (one-half of the vessel's diameter) raised to the fourth power $(R = 1/r^4)$. This means, for example, that if an artery or arteriole constricts to one-half of its original radius, the resistance to flow will increase 16 times. And if an artery or arteriole dilates to twice its initial radius, then resistance in the vessel will decrease to 1/16 of its original value and flow will increase 16 times.

The Roles of Vessel Diameter and Total Area in Blood Flow and Blood Pressure

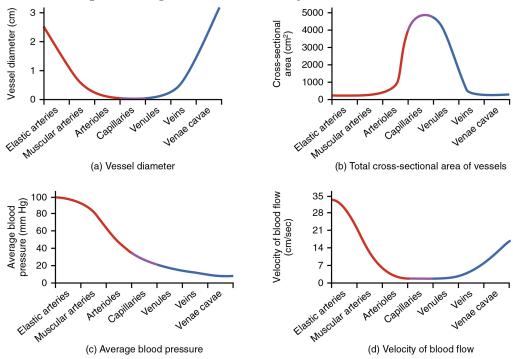
Recall that we classified arterioles as resistance vessels, because given their small lumen, they dramatically slow the flow of blood from arteries. In fact, arterioles are the site of greatest resistance in the entire vascular network. This may seem surprising, given that capillaries have a smaller size. How can this phenomenon be explained?

[link] compares vessel diameter, total cross-sectional area, average blood pressure, and blood velocity through the systemic vessels. Notice in parts (a) and (b) that the total cross-sectional area of the body's capillary beds is far greater than any other type of vessel. Although the diameter of an individual capillary is significantly smaller than the diameter of an arteriole, there are vastly more capillaries in the body than there are other types of blood vessels. Part (c) shows that blood pressure drops unevenly as blood travels from arteries to arterioles, capillaries, venules, and veins, and encounters greater resistance. However, the site of the most precipitous drop, and the site of greatest resistance, is the arterioles. This explains why vasodilation and vasoconstriction of arterioles play more significant roles in

regulating blood pressure than do the vasodilation and vasoconstriction of other vessels.

Part (d) shows that the velocity (speed) of blood flow decreases dramatically as the blood moves from arteries to arterioles to capillaries. This slow flow rate allows more time for exchange processes to occur. As blood flows through the veins, the rate of velocity increases, as blood is returned to the heart.

Relationships among Vessels in the Systemic Circuit



The relationships among blood vessels that can be compared include (a) vessel diameter, (b) total cross-sectional area, (c) average blood pressure, and (d) velocity of blood flow.

Note:

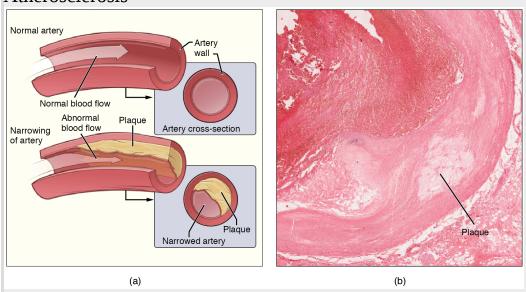
Disorders of the...

Cardiovascular System: Arteriosclerosis

Compliance allows an artery to expand when blood is pumped through it from the heart, and then to recoil after the surge has passed. This helps promote blood flow. In arteriosclerosis, compliance is reduced, and pressure and resistance within the vessel increase. This is a leading cause of hypertension and coronary heart disease, as it causes the heart to work harder to generate a pressure great enough to overcome the resistance. Arteriosclerosis begins with injury to the endothelium of an artery, which may be caused by irritation from high blood glucose, infection, tobacco use, excessive blood lipids, and other factors. Artery walls that are constantly stressed by blood flowing at high pressure are also more likely to be injured—which means that hypertension can promote arteriosclerosis, as well as result from it.

Recall that tissue injury causes inflammation. As inflammation spreads into the artery wall, it weakens and scars it, leaving it stiff (sclerotic). As a result, compliance is reduced. Moreover, circulating triglycerides and cholesterol can seep between the damaged lining cells and become trapped within the artery wall, where they are frequently joined by leukocytes, calcium, and cellular debris. Eventually, this buildup, called plaque, can narrow arteries enough to impair blood flow. The term for this condition, atherosclerosis (athero- = "porridge") describes the mealy deposits ([link]).

Atherosclerosis



(a) Atherosclerosis can result from plaques formed by the buildup of fatty, calcified deposits in an artery. (b) Plaques can also take other forms, as shown in this micrograph of a

coronary artery that has a buildup of connective tissue within the artery wall. LM \times 40. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Sometimes a plaque can rupture, causing microscopic tears in the artery wall that allow blood to leak into the tissue on the other side. When this happens, platelets rush to the site to clot the blood. This clot can further obstruct the artery and—if it occurs in a coronary or cerebral artery—cause a sudden heart attack or stroke. Alternatively, plaque can break off and travel through the bloodstream as an embolus until it blocks a more distant, smaller artery.

Even without total blockage, vessel narrowing leads to ischemia—reduced blood flow—to the tissue region "downstream" of the narrowed vessel. Ischemia in turn leads to hypoxia—decreased supply of oxygen to the tissues. Hypoxia involving cardiac muscle or brain tissue can lead to cell death and severe impairment of brain or heart function.

A major risk factor for both arteriosclerosis and atherosclerosis is advanced age, as the conditions tend to progress over time. Arteriosclerosis is normally defined as the more generalized loss of compliance, "hardening of the arteries," whereas atherosclerosis is a more specific term for the build-up of plaque in the walls of the vessel and is a specific type of arteriosclerosis. There is also a distinct genetic component, and pre-existing hypertension and/or diabetes also greatly increase the risk. However, obesity, poor nutrition, lack of physical activity, and tobacco use all are major risk factors.

Treatment includes lifestyle changes, such as weight loss, smoking cessation, regular exercise, and adoption of a diet low in sodium and saturated fats. Medications to reduce cholesterol and blood pressure may be prescribed. For blocked coronary arteries, surgery is warranted. In angioplasty, a catheter is inserted into the vessel at the point of narrowing, and a second catheter with a balloon-like tip is inflated to widen the opening. To prevent subsequent collapse of the vessel, a small mesh tube called a stent is often inserted. In an endarterectomy, plaque is surgically removed from the walls of a vessel. This operation is typically performed on the carotid arteries of the neck, which are a prime source of oxygenated

blood for the brain. In a coronary bypass procedure, a non-vital superficial vessel from another part of the body (often the great saphenous vein) or a synthetic vessel is inserted to create a path around the blocked area of a coronary artery.

Venous System

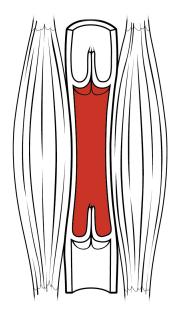
The pumping action of the heart propels the blood into the arteries, from an area of higher pressure toward an area of lower pressure. If blood is to flow from the veins back into the heart, the pressure in the veins must be greater than the pressure in the atria of the heart. Two factors help maintain this pressure gradient between the veins and the heart. First, the pressure in the atria during diastole is very low, often approaching zero when the atria are relaxed (atrial diastole). Second, two physiologic "pumps" increase pressure in the venous system. The use of the term "pump" implies a physical device that speeds flow. These physiological pumps are less obvious.

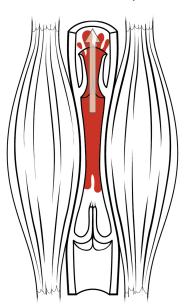
Skeletal Muscle Pump

In many body regions, the pressure within the veins can be increased by the contraction of the surrounding skeletal muscle. This mechanism, known as the **skeletal muscle pump** ([link]), helps the lower-pressure veins counteract the force of gravity, increasing pressure to move blood back to the heart. As leg muscles contract, for example during walking or running, they exert pressure on nearby veins with their numerous one-way valves. This increased pressure causes blood to flow upward, opening valves superior to the contracting muscles so blood flows through. Simultaneously, valves inferior to the contracting muscles close; thus, blood should not seep back downward toward the feet. Military recruits are trained to flex their legs slightly while standing at attention for prolonged periods. Failure to do so may allow blood to pool in the lower limbs rather than returning to the heart. Consequently, the brain will not receive enough oxygenated blood, and the individual may lose consciousness.

Skeletal Muscle Pump







The contraction of skeletal muscles surrounding a vein compresses the blood and increases the pressure in that area. This action forces blood closer to the heart where venous pressure is lower. Note the importance of the one-way valves to assure that blood flows only in the proper direction.

Respiratory Pump

The **respiratory pump** aids blood flow through the veins of the thorax and abdomen. During inhalation, the volume of the thorax increases, largely through the contraction of the diaphragm, which moves downward and compresses the abdominal cavity. The elevation of the chest caused by the contraction of the external intercostal muscles also contributes to the increased volume of the thorax. The volume increase causes air pressure

within the thorax to decrease, allowing us to inhale. Additionally, as air pressure within the thorax drops, blood pressure in the thoracic veins also decreases, falling below the pressure in the abdominal veins. This causes blood to flow along its pressure gradient from veins outside the thorax, where pressure is higher, into the thoracic region, where pressure is now lower. This in turn promotes the return of blood from the thoracic veins to the atria. During exhalation, when air pressure increases within the thoracic cavity, pressure in the thoracic veins increases, speeding blood flow into the heart while valves in the veins prevent blood from flowing backward from the thoracic and abdominal veins.

Pressure Relationships in the Venous System

Although vessel diameter increases from the smaller venules to the larger veins and eventually to the venae cavae (singular = vena cava), the total cross-sectional area actually decreases (see [link]a and b). The individual veins are larger in diameter than the venules, but their total number is much lower, so their total cross-sectional area is also lower.

Also notice that, as blood moves from venules to veins, the average blood pressure drops (see [link]c), but the blood velocity actually increases (see [link]). This pressure gradient drives blood back toward the heart. Again, the presence of one-way valves and the skeletal muscle and respiratory pumps contribute to this increased flow. Since approximately 64 percent of the total blood volume resides in systemic veins, any action that increases the flow of blood through the veins will increase venous return to the heart. Maintaining vascular tone within the veins prevents the veins from merely distending, dampening the flow of blood, and as you will see, vasoconstriction actually enhances the flow.

The Role of Venoconstriction in Resistance, Blood Pressure, and Flow

As previously discussed, vasoconstriction of an artery or arteriole decreases the radius, increasing resistance and pressure, but decreasing flow.

Venoconstriction, on the other hand, has a very different outcome. The walls of veins are thin but irregular; thus, when the smooth muscle in those walls constricts, the lumen becomes more rounded. The more rounded the lumen, the less surface area the blood encounters, and the less resistance the vessel offers. Vasoconstriction increases pressure within a vein as it does in an artery, but in veins, the increased pressure increases flow. Recall that the pressure in the atria, into which the venous blood will flow, is very low, approaching zero for at least part of the relaxation phase of the cardiac cycle. Thus, venoconstriction increases the return of blood to the heart. Another way of stating this is that venoconstriction increases the preload or stretch of the cardiac muscle and increases contraction.

Chapter Review

Blood flow is the movement of blood through a vessel, tissue, or organ. The slowing or blocking of blood flow is called resistance. Blood pressure is the force that blood exerts upon the walls of the blood vessels or chambers of the heart. The components of blood pressure include systolic pressure, which results from ventricular contraction, and diastolic pressure, which results from ventricular relaxation. Pulse pressure is the difference between systolic and diastolic measures, and mean arterial pressure is the "average" pressure of blood in the arterial system, driving blood into the tissues. Pulse, the expansion and recoiling of an artery, reflects the heartbeat. The variables affecting blood flow and blood pressure in the systemic circulation are cardiac output, compliance, blood volume, blood viscosity, and the length and diameter of the blood vessels. In the arterial system, vasodilation and vasoconstriction of the arterioles is a significant factor in systemic blood pressure: Slight vasodilation greatly decreases resistance and increases flow, whereas slight vasoconstriction greatly increases resistance and decreases flow. In the arterial system, as resistance increases, blood pressure increases and flow decreases. In the venous system, constriction increases blood pressure as it does in arteries; the increasing pressure helps to return blood to the heart. In addition, constriction causes the vessel lumen to become more rounded, decreasing resistance and increasing blood flow. Venoconstriction, while less important than arterial vasoconstriction, works with the skeletal muscle pump, the respiratory pump, and their valves to promote venous return to the heart.

Glossary

blood flow

movement of blood through a vessel, tissue, or organ that is usually expressed in terms of volume per unit of time

blood pressure

force exerted by the blood against the wall of a vessel or heart chamber; can be described with the more generic term hydrostatic pressure

compliance

degree to which a blood vessel can stretch as opposed to being rigid

diastolic pressure

lower number recorded when measuring arterial blood pressure; represents the minimal value corresponding to the pressure that remains during ventricular relaxation

hypervolemia

abnormally high levels of fluid and blood within the body

hypovolemia

abnormally low levels of fluid and blood within the body

hypoxia

lack of oxygen supply to the tissues

ischemia

insufficient blood flow to the tissues

Korotkoff sounds

noises created by turbulent blood flow through the vessels

mean arterial pressure (MAP)

average driving force of blood to the tissues; approximated by taking diastolic pressure and adding 1/3 of pulse pressure

pulse

alternating expansion and recoil of an artery as blood moves through the vessel; an indicator of heart rate

pulse pressure

difference between the systolic and diastolic pressures

resistance

any condition or parameter that slows or counteracts the flow of blood

respiratory pump

increase in the volume of the thorax during inhalation that decreases air pressure, enabling venous blood to flow into the thoracic region, then exhalation increases pressure, moving blood into the atria

skeletal muscle pump

effect on increasing blood pressure within veins by compression of the vessel caused by the contraction of nearby skeletal muscle

sphygmoman ometer

blood pressure cuff attached to a device that measures blood pressure

systolic pressure

larger number recorded when measuring arterial blood pressure; represents the maximum value following ventricular contraction

vascular tone

contractile state of smooth muscle in a blood vessel.

OU Human Physiology: Capillary Exchange By the end of this section, you will be able to:

- Accurately describe the forces that account for capillary exchange
- Discuss the pressures that drive filtration and reabsorption and therefore capillary exchange
- Distinguish between capillary hydrostatic pressure and blood colloid osmotic pressure, explaining the contribution of each to net filtration pressure
- Compare and contrast filtration and reabsorption with respect to capillaries
- Explain the fate of fluid that is not reabsorbed from the tissues into the vascular capillaries

The primary purpose of the cardiovascular system is to circulate gases, nutrients, wastes, and other substances to and from the cells of the body. Small molecules, such as gases, lipids, and lipid-soluble molecules, can diffuse directly through the membranes of the endothelial cells of the capillary wall. Glucose, amino acids, and ions—including sodium, potassium, calcium, and chloride—use transporters to move through specific channels in the membrane by facilitated diffusion. Glucose, ions, and larger molecules may also leave the blood through intercellular clefts. Larger molecules can pass through the pores of fenestrated capillaries, and even large plasma proteins can pass through the great gaps in the sinusoids. Some large proteins in blood plasma can move into and out of the endothelial cells packaged within vesicles by endocytosis and exocytosis. Water moves by osmosis.

Bulk Flow

The mass movement of fluids into and out of capillary beds requires a transport mechanism far more efficient than mere diffusion. This movement, often referred to as bulk flow, involves two pressure-driven mechanisms: Volumes of fluid move from an area of higher pressure in a capillary bed to an area of lower pressure in the tissues via **filtration**. In contrast, the movement of fluid from an area of higher pressure in the tissues into an area of lower pressure in the capillaries is **reabsorption**.

Two types of pressure interact to drive each of these movements: hydrostatic pressure and osmotic pressure.

Hydrostatic Pressure

The primary force driving fluid transport between the capillaries and tissues is hydrostatic pressure, which can be defined as the pressure of any fluid enclosed in a space. **Blood hydrostatic pressure** is the force exerted by the blood confined within blood vessels or heart chambers. Even more specifically, the pressure exerted by blood against the wall of a capillary is called **capillary hydrostatic pressure** (**CHP**), and is the same as capillary blood pressure. CHP is the force that drives fluid out of capillaries and into the tissues.

As fluid exits a capillary and moves into tissues, the hydrostatic pressure in the interstitial fluid correspondingly rises. This opposing hydrostatic pressure is called the **interstitial fluid hydrostatic pressure (IFHP)**. Generally, the CHP originating from the arterial pathways is considerably higher than the IFHP, because lymphatic vessels are continually absorbing excess fluid from the tissues. Thus, fluid generally moves out of the capillary and into the interstitial fluid. This process is called filtration.

Osmotic Pressure

The net pressure that drives reabsorption—the movement of fluid from the interstitial fluid back into the capillaries—is called osmotic pressure (sometimes referred to as oncotic pressure). Whereas hydrostatic pressure forces fluid out of the capillary, osmotic pressure draws fluid back in. Osmotic pressure is determined by osmotic concentration gradients, that is, the difference in the solute-to-water concentrations in the blood and tissue fluid. A region higher in solute concentration (and lower in water concentration) draws water across a semipermeable membrane from a region higher in water concentration (and lower in solute concentration).

As we discuss osmotic pressure in blood and tissue fluid, it is important to recognize that the formed elements of blood do not contribute to osmotic concentration gradients. Rather, it is the plasma proteins that play the key role. Solutes also move across the capillary wall according to their concentration gradient, but overall, the concentrations should be similar and not have a significant impact on osmosis. Because of their large size and chemical structure, plasma proteins are not truly solutes, that is, they do not dissolve but are dispersed or suspended in their fluid medium, forming a colloid rather than a solution.

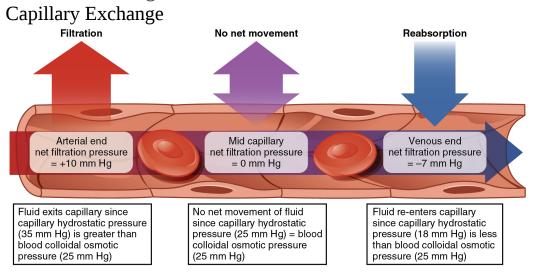
The pressure created by the concentration of colloidal proteins in the blood is called the **blood colloidal osmotic pressure (BCOP)**. Its effect on capillary exchange accounts for the reabsorption of water. The plasma proteins suspended in blood cannot move across the semipermeable capillary cell membrane, and so they remain in the plasma. As a result, blood has a higher colloidal concentration and lower water concentration than tissue fluid. It therefore attracts water. We can also say that the BCOP is higher than the **interstitial fluid colloidal osmotic pressure (IFCOP)**, which is always very low because interstitial fluid contains few proteins. Thus, water is drawn from the tissue fluid back into the capillary, carrying dissolved molecules with it. This difference in colloidal osmotic pressure accounts for reabsorption.

Interaction of Hydrostatic and Osmotic Pressures

The normal unit used to express pressures within the cardiovascular system is millimeters of mercury (mm Hg). When blood leaving an arteriole first enters a capillary bed, the CHP is quite high—about 35 mm Hg. Gradually, this initial CHP declines as the blood moves through the capillary so that by the time the blood has reached the venous end, the CHP has dropped to approximately 18 mm Hg. In comparison, the plasma proteins remain suspended in the blood, so the BCOP remains fairly constant at about 25 mm Hg throughout the length of the capillary and considerably below the osmotic pressure in the interstitial fluid.

The **net filtration pressure (NFP)** represents the interaction of the hydrostatic and osmotic pressures, driving fluid out of the capillary. It is equal to the difference between the CHP and the BCOP. Since filtration is, by definition, the movement of fluid out of the capillary, when reabsorption is occurring, the NFP is a negative number.

NFP changes at different points in a capillary bed ([link]). Close to the arterial end of the capillary, it is approximately 10 mm Hg, because the CHP of 35 mm Hg minus the BCOP of 25 mm Hg equals 10 mm Hg. Recall that the hydrostatic and osmotic pressures of the interstitial fluid are essentially negligible. Thus, the NFP of 10 mm Hg drives a net movement of fluid out of the capillary at the arterial end. At approximately the middle of the capillary, the CHP is about the same as the BCOP of 25 mm Hg, so the NFP drops to zero. At this point, there is no net change of volume: Fluid moves out of the capillary at the same rate as it moves into the capillary. Near the venous end of the capillary, the CHP has dwindled to about 18 mm Hg due to loss of fluid. Because the BCOP remains steady at 25 mm Hg, water is drawn into the capillary, that is, reabsorption occurs. Another way of expressing this is to say that at the venous end of the capillary, there is an NFP of -7 mm Hg.



Net filtration occurs near the arterial end of the capillary since capillary hydrostatic pressure (CHP) is greater than blood colloidal osmotic pressure (BCOP). There is no net movement of fluid near the midpoint since CHP = BCOP.

Net reabsorption occurs near the venous end since BCOP is greater than CHP.

The Role of Lymphatic Capillaries

Since overall CHP is higher than BCOP, it is inevitable that more net fluid will exit the capillary through filtration at the arterial end than enters through reabsorption at the venous end. Considering all capillaries over the course of a day, this can be quite a substantial amount of fluid: Approximately 24 liters per day are filtered, whereas 20.4 liters are reabsorbed. This excess fluid is picked up by capillaries of the lymphatic system. These extremely thin-walled vessels have copious numbers of valves that ensure unidirectional flow through ever-larger lymphatic vessels that eventually drain into the subclavian veins in the neck. An important function of the lymphatic system is to return the fluid (lymph) to the blood. Lymph may be thought of as recycled <u>blood plasma</u>. (Seek additional content for more detail on the lymphatic system.)

Note:



Watch this <u>video</u> to explore capillaries and how they function in the body. Capillaries are never more than 100 micrometers away. What is the main component of interstitial fluid?

Chapter Review

Small molecules can cross into and out of capillaries via simple or facilitated diffusion. Some large molecules can cross in vesicles or through clefts, fenestrations, or gaps between cells in capillary walls. However, the bulk flow of capillary and tissue fluid occurs via filtration and reabsorption. Filtration, the movement of fluid out of the capillaries, is driven by the CHP. Reabsorption, the influx of tissue fluid into the capillaries, is driven by the BCOP. Filtration predominates in the arterial end of the capillary; in the middle section, the opposing pressures are virtually identical so there is no net exchange, whereas reabsorption predominates at the venule end of the capillary. The hydrostatic and colloid osmotic pressures in the interstitial fluid are negligible in healthy circumstances.

Glossary

blood colloidal osmotic pressure (BCOP)

pressure exerted by colloids suspended in blood within a vessel; a primary determinant is the presence of plasma proteins

blood hydrostatic pressure

force blood exerts against the walls of a blood vessel or heart chamber

capillary hydrostatic pressure (CHP) force blood exerts against a capillary

filtration

in the cardiovascular system, the movement of material from a capillary into the interstitial fluid, moving from an area of higher pressure to lower pressure

interstitial fluid colloidal osmotic pressure (IFCOP) pressure exerted by the colloids within the interstitial fluid

interstitial fluid hydrostatic pressure (IFHP) force exerted by the fluid in the tissue spaces

net filtration pressure (NFP)

force driving fluid out of the capillary and into the tissue spaces; equal to the difference of the capillary hydrostatic pressure and the blood

colloidal osmotic pressure

reabsorption

in the cardiovascular system, the movement of material from the interstitial fluid into the capillaries

OU Human Physiology: Homeostatic Regulation of the Vascular System By the end of this section, you will be able to:

- Discuss the importance of reconditioning organs and how blood flow is altered to such organs
- Explain why the brain is not a reconditioning organ
- Describe how each of the cardiovascular centers contribute to the regulation of MAP
- Compare and contrast the short term regulation of MAP (baroreceptors and chemoreceptors) to long term regulation of MAP (hormones and the renin-angiotensin system) in efforts to maintain homeostasis within blood vessels
- Describe the interrelationship of the cardiovascular and respiratory controls in maintaining vascular homeostasis
- Explain the intrinsic controls involved in autoregulation of perfusion
- Discuss the common disorders that affect vascular homeostasis
- Describe the interrelationship of the cardiovascular system, lymphatic system, and the blood

In order to maintain homeostasis in the cardiovascular system and provide adequate blood to the tissues, blood flow must be redirected continually to the tissues as they become more active. In a very real sense, the cardiovascular system engages in resource allocation, because there is not enough blood flow to distribute blood equally to all tissues simultaneously. For example, when an individual is exercising, more blood will be directed to skeletal muscles, the heart, and the lungs. Following a meal, more blood is directed to the digestive organs; these organs as well as many other organs are called reconditioning organs as blood flow to them can be altered without altering function. Only the brain receives a more or less constant supply of blood whether you are active, resting, thinking, or engaged in any other activity; this constant blood supply is necessary as alteration of blood flow can damage the brain. Thus, the brain is not considered a reconditioning organ.

[link] provides the distribution of systemic blood at rest and during exercise. Although most of the data appears logical, the values for the distribution of blood to the integument may seem surprising. During

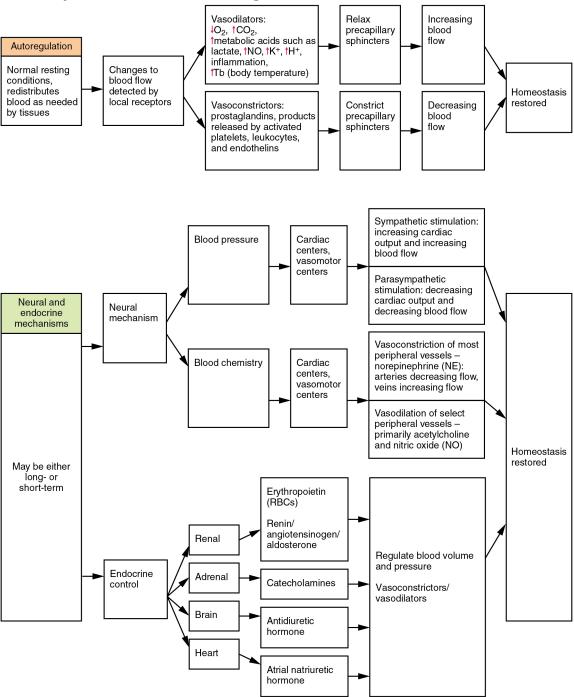
exercise, the body distributes more blood to the body surface where it can dissipate the excess heat generated by increased activity into the environment.

Systemic Blood Flow During Rest, Mild Exercise, and Maximal
Exercise in a Healthy Young Individual

Organ	Resting (mL/min)	Mild exercise (mL/min)	Maximal exercise (mL/min)
Skeletal muscle	1200	4500	12,500
Heart	250	350	750
Brain	750	750	750
Integument	500	1500	1900
Kidney	1100	900	600
Gastrointestinal	1400	1100	600
Others (i.e., liver, spleen)	600	400	400
Total	5800	9500	17,500

Three homeostatic mechanisms ensure adequate blood flow, blood pressure, distribution, and ultimately perfusion: neural, endocrine, and autoregulatory mechanisms. They are summarized in [link].

Summary of Factors Maintaining Vascular Homeostasis



Adequate blood flow, blood pressure, distribution, and perfusion involve autoregulatory, neural, and endocrine mechanisms.

Neural Regulation

The nervous system plays a critical role in the regulation of vascular homeostasis. The primary regulatory sites include the cardiovascular centers in the brain that control both cardiac and vascular functions. In addition, more generalized neural responses from the limbic system and the autonomic nervous system are factors.

The Cardiovascular Centers in the Brain

Neurological regulation of blood pressure and flow depends on the cardiovascular centers located in the medulla oblongata. This cluster of neurons responds to changes in blood pressure as well as blood concentrations of oxygen, carbon dioxide, and hydrogen ions. The cardiovascular center contains three distinct paired components:

- The cardioaccelerator centers stimulate cardiac function by regulating heart rate and stroke volume via sympathetic stimulation from the cardiac accelerator nerve.
- The cardioinhibitor centers slow cardiac function by decreasing heart rate and stroke volume via parasympathetic stimulation from the vagus nerve.
- The vasomotor centers control vessel tone or contraction of the smooth muscle in the tunica media. Changes in diameter affect peripheral resistance, pressure, and flow, which affect cardiac output. The majority of these neurons act via the release of the neurotransmitter norepinephrine from sympathetic neurons.

Although each center functions independently, they are not anatomically distinct.

There is also a small population of neurons that control vasodilation in the vessels of the brain and skeletal muscles by relaxing the smooth muscle fibers in the vessel tunics. Many of these are cholinergic neurons, that is, they release acetylcholine, which in turn stimulates the vessels' endothelial cells to release nitric oxide (NO), which causes vasodilation. Others release

norepinephrine that binds to β_2 receptors. A few neurons release NO directly as a neurotransmitter.

Recall that mild stimulation of the skeletal muscles maintains muscle tone. A similar phenomenon occurs with vascular tone in vessels. As noted earlier, arterioles are normally partially constricted: With maximal stimulation, their radius may be reduced to one-half of the resting state. Full dilation of most arterioles requires that this sympathetic stimulation be suppressed. When it is, an arteriole can expand by as much as 150 percent. Such a significant increase can dramatically affect resistance, pressure, and flow.

Baroreceptor Reflexes

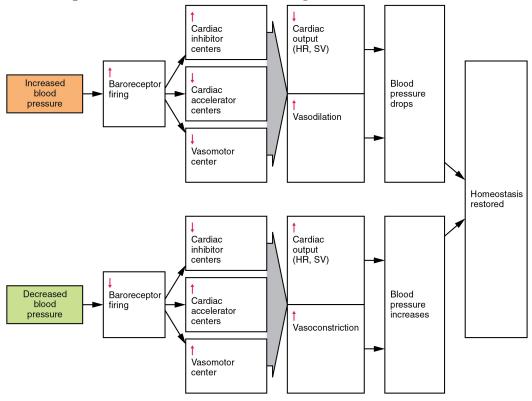
Baroreceptors are specialized stretch receptors located within areas of blood vessels and heart chambers that respond to the degree of stretch caused by the presence of blood. They send impulses to the cardiovascular center to regulate blood pressure. This is often referred to as a short-term regulation of mean arterial pressure (MAP). Vascular baroreceptors are found primarily in sinuses (small cavities) within the aorta and carotid arteries: The **aortic sinuses** are found in the walls of the aorta, whereas the **carotid sinuses** are in the walls of the carotid arteries. There are also low-pressure baroreceptors located in the walls of the venae cavae and right atrium. Here we will focus our attention on the carotid and aortic baroreceptors.

When blood pressure increases, the baroreceptors are stretched more tightly and initiate action potentials at a higher rate. At lower blood pressures, the degree of stretch is lower and the rate of firing is slower. When the cardiovascular center in the medulla oblongata receives this input, it triggers a reflex that maintains homeostasis ([link]):

• When blood pressure rises too high, the baroreceptors fire at a higher rate and trigger parasympathetic stimulation of the heart. As a result, cardiac output falls. Sympathetic stimulation of the peripheral arterioles will also decrease, resulting in vasodilation. Combined, these activities cause blood pressure to fall.

 When blood pressure drops too low, the rate of baroreceptor firing decreases. This will trigger an increase in sympathetic stimulation of the heart, causing cardiac output to increase. It will also trigger sympathetic stimulation of the peripheral vessels, resulting in vasoconstriction. Combined, these activities cause blood pressure to rise.

Baroreceptor Reflexes for Maintaining Vascular Homeostasis



Increased blood pressure results in increased rates of baroreceptor firing, whereas decreased blood pressure results in slower rates of fire, both initiating the homeostatic mechanism to restore blood pressure.

The baroreceptors in the venae cavae and right atrium monitor blood pressure as the blood returns to the heart from the systemic circulation. Normally, blood flow into the aorta is the same as blood flow back into the right atrium. If blood is returning to the right atrium more rapidly than it is

being ejected from the left ventricle, the atrial receptors will stimulate the cardiovascular centers to increase sympathetic firing and increase cardiac output until homeostasis is achieved. The opposite is also true. This mechanism is referred to as the atrial reflex.

Chemoreceptor Reflexes

In addition to the baroreceptors are chemoreceptors that monitor levels of oxygen, carbon dioxide, and hydrogen ions (pH), and thereby contribute to vascular homeostasis. Chemoreceptors monitoring the blood are located in close proximity to the baroreceptors in the aortic and carotid sinuses. They signal the cardiovascular center as well as the respiratory centers in the medulla oblongata.

Since tissues consume oxygen and produce carbon dioxide and acids as waste products, when the body is more active, oxygen levels fall and carbon dioxide levels rise as cells undergo cellular respiration to meet the energy needs of activities. This causes more hydrogen ions to be produced, causing the blood pH to drop. When the body is resting, oxygen levels are higher, carbon dioxide levels are lower, more hydrogen is bound, and pH rises. (Seek additional content for more detail about pH.)

The chemoreceptors respond to increasing carbon dioxide and hydrogen ion levels (falling pH) by stimulating the cardioaccelerator and vasomotor centers, increasing cardiac output and constricting peripheral vessels. The cardioinhibitor centers are suppressed. With falling carbon dioxide and hydrogen ion levels (increasing pH), the cardioinhibitor centers are stimulated, and the cardioaccelerator and vasomotor centers are suppressed, decreasing cardiac output and causing peripheral vasodilation. In order to maintain adequate supplies of oxygen to the cells and remove waste products such as carbon dioxide, it is essential that the respiratory system respond to changing metabolic demands. In turn, the cardiovascular system will transport these gases to the lungs for exchange, again in accordance with metabolic demands. This interrelationship of cardiovascular and respiratory control cannot be overemphasized.

Other neural mechanisms can also have a significant impact on cardiovascular function. These include the limbic system that links physiological responses to psychological stimuli, as well as generalized sympathetic and parasympathetic stimulation.

Endocrine Regulation

Endocrine control over the cardiovascular system involves the catecholamines, epinephrine and norepinephrine, as well as several hormones that interact with the kidneys in the regulation of blood volume.

Epinephrine and Norepinephrine

The catecholamines epinephrine and norepinephrine are released by the adrenal medulla, and enhance and extend the body's sympathetic or "fight-or-flight" response (see [link]). They increase heart rate and force of contraction, while temporarily constricting blood vessels to organs not essential for flight-or-fight responses and redirecting blood flow to the liver, muscles, and heart.

Antidiuretic Hormone

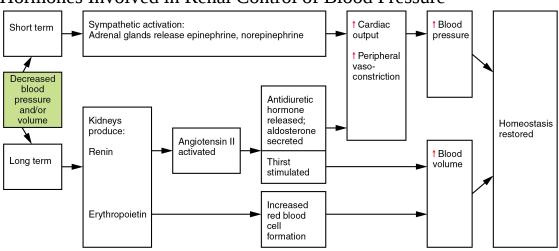
Antidiuretic hormone (ADH), also known as vasopressin, is secreted by the cells in the hypothalamus and transported via the hypothalamic-hypophyseal tracts to the posterior pituitary where it is stored until released upon nervous stimulation. The primary trigger prompting the hypothalamus to release ADH is increasing osmolarity of tissue fluid, usually in response to significant loss of blood volume. ADH signals its target cells in the kidneys to reabsorb more water, thus preventing the loss of additional fluid in the urine. This will increase overall fluid levels and help restore blood volume and pressure. In addition, ADH constricts peripheral vessels.

Renin-Angiotensin-Aldosterone Mechanism

The renin-angiotensin-aldosterone mechanism has a major effect upon the cardiovascular system ([link]). Renin is an enzyme, although because of its importance in the renin-angiotensin-aldosterone pathway, some sources identify it as a hormone. Specialized cells in the kidneys found in the juxtaglomerular apparatus respond to decreased blood flow and therefore decreased MAP by secreting renin into the blood. Renin converts the plasma protein angiotensinogen, which is produced by the liver, into its active form—angiotensin I. Angiotensin I circulates in the blood and is then converted into angiotensin II in the lungs. This reaction is catalyzed by the enzyme angiotensin-converting enzyme (ACE).

Angiotensin II is a powerful vasoconstrictor, greatly increasing blood pressure. It also stimulates the release of ADH and aldosterone, a hormone produced by the adrenal cortex. Aldosterone increases the reabsorption of sodium into the blood by the kidneys. Since water follows sodium, this increases the reabsorption of water. This in turn increases blood volume, raising blood pressure. Angiotensin II also stimulates the thirst center in the hypothalamus, so an individual will likely consume more fluids, again increasing blood volume and pressure.

Hormones Involved in Renal Control of Blood Pressure



In the renin-angiotensin-aldosterone mechanism, increasing angiotensin II will stimulate the production of antidiuretic hormone and aldosterone. In addition to renin, the kidneys produce erythropoietin, which stimulates the production of red blood cells, further increasing blood volume.

Erythropoietin

Erythropoietin (EPO) is released by the kidneys when blood flow and/or oxygen levels decrease. EPO stimulates the production of erythrocytes within the bone marrow. Erythrocytes are the major formed element of the blood and may contribute 40 percent or more to blood volume, a significant factor of viscosity, resistance, pressure, and flow. In addition, EPO is a vasoconstrictor. Overproduction of EPO or excessive intake of synthetic EPO, often to enhance athletic performance, will increase viscosity, resistance, and pressure, and decrease flow in addition to its contribution as a vasoconstrictor.

Atrial Natriuretic Hormone

Secreted by cells in the atria of the heart, atrial natriuretic hormone (ANH) (also known as atrial natriuretic peptide) is secreted when blood volume is high enough to cause extreme stretching of the cardiac cells. Cells in the ventricle produce a hormone with similar effects, called B-type natriuretic hormone. Natriuretic hormones are antagonists to angiotensin II. They promote loss of sodium and water from the kidneys, and suppress renin, aldosterone, and ADH production and release. All of these actions promote loss of fluid from the body, so blood volume and blood pressure drop.

Autoregulation of Perfusion

As the name would suggest, autoregulation mechanisms require neither specialized nervous stimulation nor endocrine control. Rather, these are local, self-regulatory mechanisms that allow each region of tissue to adjust

its blood flow—and thus its perfusion. These local mechanisms include chemical signals and myogenic controls.

Chemical Signals Involved in Autoregulation

Chemical signals work at the level of the precapillary sphincters to trigger either constriction or relaxation. As you know, opening a precapillary sphincter allows blood to flow into that particular capillary, whereas constricting a precapillary sphincter temporarily shuts off blood flow to that region. The factors involved in regulating the precapillary sphincters include the following:

- Opening of the sphincter is triggered in response to decreased oxygen concentrations; increased carbon dioxide concentrations; increasing levels of lactic acid or other byproducts of cellular metabolism; increasing concentrations of potassium ions or hydrogen ions (falling pH); inflammatory chemicals such as histamines; and increased body temperature. These conditions in turn stimulate the release of NO, a powerful vasodilator, from endothelial cells (see [link]).
- Contraction of the precapillary sphincter is triggered by the opposite levels of the regulators, which prompt the release of endothelins, powerful vasoconstricting peptides secreted by endothelial cells.
 Platelet secretions and certain prostaglandins may also trigger constriction.

Again, these factors alter tissue perfusion via their effects on the precapillary sphincter mechanism, which regulates blood flow to capillaries. Since the amount of blood is limited, not all capillaries can fill at once, so blood flow is allocated based upon the needs and metabolic state of the tissues as reflected in these parameters. Bear in mind, however, that dilation and constriction of the arterioles feeding the capillary beds is the primary control mechanism.

The **myogenic response** is a reaction to the stretching of the smooth muscle in the walls of arterioles as changes in blood flow occur through the vessel. This may be viewed as a largely protective function against dramatic fluctuations in blood pressure and blood flow to maintain homeostasis. If perfusion of an organ is too low (ischemia), the tissue will experience low levels of oxygen (hypoxia). In contrast, excessive perfusion could damage the organ's smaller and more fragile vessels. The myogenic response is a localized process that serves to stabilize blood flow in the capillary network that follows that arteriole.

When blood flow is low, the vessel's smooth muscle will be only minimally stretched. In response, it relaxes, allowing the vessel to dilate and thereby increase the movement of blood into the tissue. When blood flow is too high, the smooth muscle will contract in response to the increased stretch, prompting vasoconstriction that reduces blood flow.

[link] summarizes the effects of nervous, endocrine, and local controls on arterioles.

Summary of Mechanisms Regulating Arteriole Smooth Muscle and Veins

Control	Factor	Vasoconstriction	Vasodilation
Neural	Sympathetic stimulation	Arterioles within integument, abdominal viscera, and mucosa membrane; skeletal muscle (at high levels); varied in veins and venules	Arterioles within heart; skeletal muscles at low to moderate levels
	Parasympathetic	No known innervation for most	Arterioles in external genitalia, no known innervation for most other arterioles or veins
Endocrine	Epinephrine	Similar to sympathetic stimulation for extended flight-or-fight responses; at high levels, binds to specialized alpha (α) receptors	Similar to sympathetic stimulation for extended fight-or-flight responses; at low to moderate levels, binds to specialized beta (β) receptors
	Norepinephrine	Similar to epinephrine	Similar to epinephrine
	Angiotensin II	Powerful generalized vasoconstrictor; also stimulates release of aldosterone and ADH	n/a
	ANH (peptide)	n/a	Powerful generalized vasodilator; also promotes loss of fluid volume from kidneys, hence reducing blood volume, pressure, and flow
	ADH	Moderately strong generalized vasoconstrictor; also causes body to retain more fluid via kidneys, increasing blood volume and pressure	n/a
Other factors	Decreasing levels of oxygen	n/a	Vasodilation, also opens precapillary sphincters
	Decreasing pH	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of carbon dioxide	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of potassium ion	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of prostaglandins	Vasoconstriction, closes precapillary sphincters for many	Vasodilation, opens precapillary sphincters for many
	Increasing levels of adenosine	n/a	Vasodilation
	Increasing levels of NO	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of lactic acid and other metabolites	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of endothelins	Vasoconstriction	n/a
	Increasing levels of platelet secretions	Vasoconstriction	n/a
	Increasing hyperthermia	n/a	Vasodilation
	Stretching of vascular wall (myogenic)	Vasoconstriction	n/a
	Increasing levels of histamines from basophils and mast cells	n/a	Vasodilation

Effect of Exercise on Vascular Homeostasis

The heart is a muscle and, like any muscle, it responds dramatically to exercise. For a healthy young adult, cardiac output (heart rate × stroke volume) increases in the nonathlete from approximately 5.0 liters (5.25 quarts) per minute to a maximum of about 20 liters (21 quarts) per minute. Accompanying this will be an increase in blood pressure from about 120/80 to 185/75. However, well-trained aerobic athletes can increase these values

substantially. For these individuals, cardiac output soars from approximately 5.3 liters (5.57 quarts) per minute resting to more than 30 liters (31.5 quarts) per minute during maximal exercise. Along with this increase in cardiac output, blood pressure increases from 120/80 at rest to 200/90 at maximum values.

In addition to improved cardiac function, exercise increases the size and mass of the heart. The average weight of the heart for the nonathlete is about 300 g, whereas in an athlete it will increase to 500 g. This increase in size generally makes the heart stronger and more efficient at pumping blood, increasing both stroke volume and cardiac output.

Tissue perfusion also increases as the body transitions from a resting state to light exercise and eventually to heavy exercise (see [link]). These changes result in selective vasodilation in the skeletal muscles, heart, lungs, liver, and integument. Simultaneously, vasoconstriction occurs in the vessels leading to the kidneys and most of the digestive and reproductive organs. The flow of blood to the brain remains largely unchanged whether at rest or exercising, since the vessels in the brain largely do not respond to regulatory stimuli, in most cases, because they lack the appropriate receptors.

As vasodilation occurs in selected vessels, resistance drops and more blood rushes into the organs they supply. This blood eventually returns to the venous system. Venous return is further enhanced by both the skeletal muscle and respiratory pumps. As blood returns to the heart more quickly, preload rises and the Frank-Starling principle tells us that contraction of the cardiac muscle in the atria and ventricles will be more forceful. Eventually, even the best-trained athletes will fatigue and must undergo a period of rest following exercise. Cardiac output and distribution of blood then return to normal.

Regular exercise promotes cardiovascular health in a variety of ways. Because an athlete's heart is larger than a nonathlete's, stroke volume increases, so the athletic heart can deliver the same amount of blood as the nonathletic heart but with a lower heart rate. This increased efficiency allows the athlete to exercise for longer periods of time before muscles fatigue and places less stress on the heart. Exercise also lowers overall

cholesterol levels by removing from the circulation a complex form of cholesterol, triglycerides, and proteins known as low-density lipoproteins (LDLs), which are widely associated with increased risk of cardiovascular disease. Although there is no way to remove deposits of plaque from the walls of arteries other than specialized surgery, exercise does promote the health of vessels by decreasing the rate of plaque formation and reducing blood pressure, so the heart does not have to generate as much force to overcome resistance.

Generally as little as 30 minutes of noncontinuous exercise over the course of each day has beneficial effects and has been shown to lower the rate of heart attack by nearly 50 percent. While it is always advisable to follow a healthy diet, stop smoking, and lose weight, studies have clearly shown that fit, overweight people may actually be healthier overall than sedentary slender people. Thus, the benefits of moderate exercise are undeniable.

Clinical Considerations in Vascular Homeostasis

Any disorder that affects blood volume, vascular tone, or any other aspect of vascular functioning is likely to affect vascular homeostasis as well. That includes hypertension, hemorrhage, and shock.

Hypertension and Hypotension

Chronically elevated blood pressure is known clinically as **hypertension**. It is defined as chronic and persistent blood pressure measurements of 140/90 mm Hg or above. Pressures between 120/80 and 140/90 mm Hg are defined as prehypertension. About 68 million Americans currently suffer from hypertension. Unfortunately, hypertension is typically a silent disorder; therefore, hypertensive patients may fail to recognize the seriousness of their condition and fail to follow their treatment plan. The result is often a heart attack or stroke. Hypertension may also lead to an aneurism (ballooning of a blood vessel caused by a weakening of the wall), peripheral arterial disease (obstruction of vessels in peripheral regions of the body), chronic kidney disease, or heart failure.

Note:



Listen to this CDC <u>podcast</u> to learn about hypertension, often described as a "silent killer." What steps can you take to reduce your risk of a heart attack or stroke?

Hemorrhage

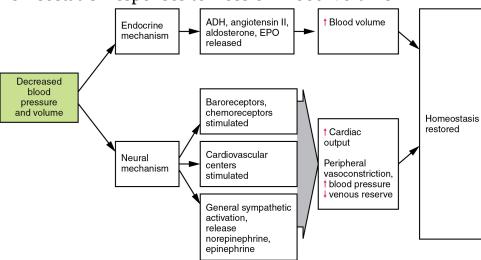
Minor blood loss is managed by hemostasis and repair. Hemorrhage is a loss of blood that cannot be controlled by hemostatic mechanisms. Initially, the body responds to hemorrhage by initiating mechanisms aimed at increasing blood pressure and maintaining blood flow. Ultimately, however, blood volume will need to be restored, either through physiological processes or through medical intervention.

In response to blood loss, stimuli from the baroreceptors trigger the cardiovascular centers to stimulate sympathetic responses to increase cardiac output and vasoconstriction. This typically prompts the heart rate to increase to about 180–200 contractions per minute, restoring cardiac output to normal levels. Vasoconstriction of the arterioles increases vascular resistance, whereas constriction of the veins increases venous return to the heart. Both of these steps will help increase blood pressure. Sympathetic stimulation also triggers the release of epinephrine and norepinephrine, which enhance both cardiac output and vasoconstriction. If blood loss were less than 20 percent of total blood volume, these responses together would usually return blood pressure to normal and redirect the remaining blood to the tissues.

Additional endocrine involvement is necessary, however, to restore the lost blood volume. The angiotensin-renin-aldosterone mechanism stimulates the

thirst center in the hypothalamus, which increases fluid consumption to help restore the lost blood. More importantly, it increases renal reabsorption of sodium and water, reducing water loss in urine output. The kidneys also increase the production of EPO, stimulating the formation of erythrocytes that not only deliver oxygen to the tissues but also increase overall blood volume. [link] summarizes the responses to loss of blood volume.

Homeostatic Responses to Loss of Blood Volume



Circulatory Shock

The loss of too much blood may lead to **circulatory shock**, a lifethreatening condition in which the circulatory system is unable to maintain blood flow to adequately supply sufficient oxygen and other nutrients to the tissues to maintain cellular metabolism. It should not be confused with emotional or psychological shock. Typically, the patient in circulatory shock will demonstrate an increased heart rate but decreased blood pressure, but there are cases in which blood pressure will remain normal. Urine output will fall dramatically, and the patient may appear confused or lose consciousness. Urine output less than 1 mL/kg body weight/hour is cause for concern. Unfortunately, shock is an example of a positive-feedback loop that, if uncorrected, may lead to the death of the patient.

There are several recognized forms of shock:

- Hypovolemic shock in adults is typically caused by hemorrhage, although in children it may be caused by fluid losses related to severe vomiting or diarrhea. Other causes for hypovolemic shock include extensive burns, exposure to some toxins, and excessive urine loss related to diabetes insipidus or ketoacidosis. Typically, patients present with a rapid, almost tachycardic heart rate; a weak pulse often described as "thread;" cool, clammy skin, particularly in the extremities, due to restricted peripheral blood flow; rapid, shallow breathing; hypothermia; thirst; and dry mouth. Treatments generally involve providing intravenous fluids to restore the patient to normal function and various drugs such as dopamine, epinephrine, and norepinephrine to raise blood pressure.
- Cardiogenic shock results from the inability of the heart to maintain cardiac output. Most often, it results from a myocardial infarction (heart attack), but it may also be caused by arrhythmias, valve disorders, cardiomyopathies, cardiac failure, or simply insufficient flow of blood through the cardiac vessels. Treatment involves repairing the damage to the heart or its vessels to resolve the underlying cause, rather than treating cardiogenic shock directly.
- Vascular shock occurs when arterioles lose their normal muscular tone and dilate dramatically. It may arise from a variety of causes, and treatments almost always involve fluid replacement and medications, called inotropic or pressor agents, which restore tone to the muscles of the vessels. In addition, eliminating or at least alleviating the underlying cause of the condition is required. This might include antibiotics and antihistamines, or select steroids, which may aid in the repair of nerve damage. A common cause is **sepsis** (or septicemia), also called "blood poisoning," which is a widespread bacterial infection that results in an organismal-level inflammatory response known as **septic shock**. **Neurogenic shock** is a form of vascular shock that occurs with cranial or spinal injuries that damage the cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region. **Anaphylactic shock** is a severe allergic response that causes the widespread release of histamines, triggering vasodilation throughout the body.
- **Obstructive shock**, as the name would suggest, occurs when a significant portion of the vascular system is blocked. It is not always

recognized as a distinct condition and may be grouped with cardiogenic shock, including pulmonary embolism and cardiac tamponade. Treatments depend upon the underlying cause and, in addition to administering fluids intravenously, often include the administration of anticoagulants, removal of fluid from the pericardial cavity, or air from the thoracic cavity, and surgery as required. The most common cause is a pulmonary embolism, a clot that lodges in the pulmonary vessels and interrupts blood flow. Other causes include stenosis of the aortic valve; cardiac tamponade, in which excess fluid in the pericardial cavity interferes with the ability of the heart to fully relax and fill with blood (resulting in decreased preload); and a pneumothorax, in which an excessive amount of air is present in the thoracic cavity, outside of the lungs, which interferes with venous return, pulmonary function, and delivery of oxygen to the tissues.

Chapter Review

Neural, endocrine, and autoregulatory mechanisms affect blood flow, blood pressure, and eventually perfusion of blood to body tissues. Neural mechanisms include the cardiovascular centers in the medulla oblongata, baroreceptors in the aorta and carotid arteries and right atrium, and associated chemoreceptors that monitor blood levels of oxygen, carbon dioxide, and hydrogen ions. Endocrine controls include epinephrine and norepinephrine, as well as ADH, the renin-angiotensin-aldosterone mechanism, ANH, and EPO. Autoregulation is the local control of vasodilation and constriction by chemical signals and the myogenic response. Exercise greatly improves cardiovascular function and reduces the risk of cardiovascular diseases, including hypertension, a leading cause of heart attacks and strokes. Significant hemorrhage can lead to a form of circulatory shock known as hypovolemic shock. Sepsis, obstruction, and widespread inflammation can also cause circulatory shock.

Glossary

anaphylactic shock

type of shock that follows a severe allergic reaction and results from massive vasodilation

aortic sinuses

small pockets in the ascending aorta near the aortic valve that are the locations of the baroreceptors (stretch receptors) and chemoreceptors that trigger a reflex that aids in the regulation of vascular homeostasis

cardiogenic shock

type of shock that results from the inability of the heart to maintain cardiac output

carotid sinuses

small pockets near the base of the internal carotid arteries that are the locations of the baroreceptors and chemoreceptors that trigger a reflex that aids in the regulation of vascular homeostasis

circulatory shock

also simply called shock; a life-threatening medical condition in which the circulatory system is unable to supply enough blood flow to provide adequate oxygen and other nutrients to the tissues to maintain cellular metabolism

hypertension

chronic and persistent blood pressure measurements of 140/90 mm Hg or above

hypovolemic shock

type of circulatory shock caused by excessive loss of blood volume due to hemorrhage or possibly dehydration

myogenic response

constriction or dilation in the walls of arterioles in response to pressures related to blood flow; reduces high blood flow or increases low blood flow to help maintain consistent flow to the capillary network

neurogenic shock

type of shock that occurs with cranial or high spinal injuries that damage the cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region

obstructive shock

type of shock that occurs when a significant portion of the vascular system is blocked

sepsis

(also, septicemia) organismal-level inflammatory response to a massive infection

septic shock

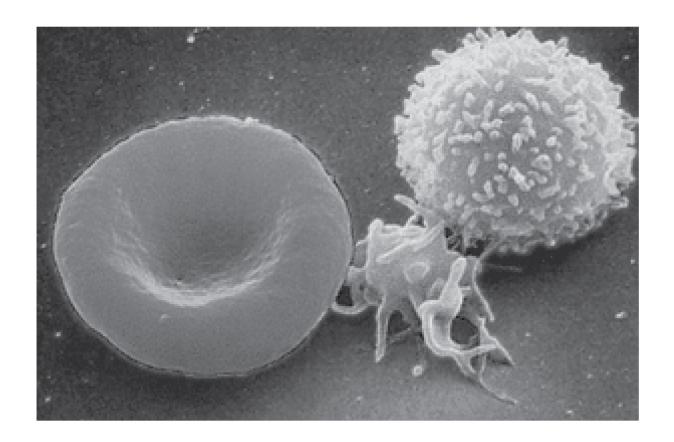
(also, blood poisoning) type of shock that follows a massive infection resulting in organism-wide inflammation

vascular shock

type of shock that occurs when arterioles lose their normal muscular tone and dilate dramatically

OU Human Physiology: Blood Introduction class="introduction" Blood Cells

A single drop of blood contains millions of red blood cells, white blood cells, and platelets. One of each type is shown here, isolated from a scanning electron micrograph



Note:

Chapter Objectives
After studying this chapter, you will be able to:

Single-celled organisms do not need blood. They obtain nutrients directly from and excrete wastes directly into their environment. The human organism cannot do that. Our large, complex bodies need blood to deliver nutrients to and remove wastes from our trillions of cells. The heart pumps blood throughout the body in a network of blood vessels. Together, these three components—blood, heart, and vessels—makes up the cardiovascular system. This chapter focuses on the medium of transport: blood.

OU Human Physiology: An Overview of Blood By the end of this section, you will be able to:

- Identify the primary functions of blood, its fluid and cellular components, in transportation, defense, and maintenance of homeostasis
- Name the fluid component of blood and the three major types of formed elements, and identify their relative proportions in a blood sample
- Discuss the unique physical characteristics of blood
- Identify the composition of blood plasma, including its most important solutes and plasma proteins

Recall that **blood** is a connective tissue. Like all connective tissues, it is made up of cellular elements and an extracellular matrix. The cellular elements—referred to as the **formed elements**—include **red blood cells (RBCs)**, **white blood cells (WBCs)**, and cell fragments called **platelets**. The extracellular matrix, called **plasma**, makes blood unique among connective tissues because it is fluid. This fluid, which is mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body.

Moreover, endocrine glands scattered throughout the body release their products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body, and various waste products are transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Recall that body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the pH of body tissues. Blood also helps to regulate the water content of body cells.

Composition of Blood

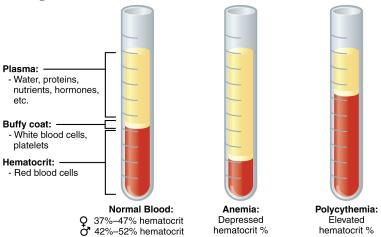
You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements.

One such test, called a **hematocrit**, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma ([link]). Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the WBCs, clinically known as leukocytes, and the platelets, cell fragments also called thrombocytes. This layer is referred to as the **buffy coat** because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

The volume of erythrocytes after centrifugation is also commonly referred to as **packed cell volume (PCV)**. In normal blood, about 45 percent of a sample is erythrocytes. The hematocrit of any one sample can vary significantly, however, about 36–50 percent, according to gender and other factors. Normal hematocrit values for females range from 37 to 47, with a mean value of 41; for males, hematocrit ranges from 42 to 52, with a mean of 47. The percentage of other formed elements, the WBCs and platelets, is extremely small. So the mean plasma percentage is the percent of blood that

is not erythrocytes: for females, it is approximately 59 (or 100 minus 41), and for males, it is approximately 53 (or 100 minus 47).

Composition of Blood



The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison.

Characteristics of Blood

When you think about blood, the first characteristic that probably comes to mind is its color. Blood that has just taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a more dusky red.

This is because hemoglobin is a pigment that changes color, depending upon the degree of oxygen saturation.

Blood is viscous and somewhat sticky to the touch. It has a viscosity approximately five times greater than water. Viscosity is a measure of a fluid's thickness or resistance to flow, and is influenced by the presence of the plasma proteins and formed elements within the blood. The viscosity of blood has a dramatic impact on blood pressure and flow. Consider the difference in flow between water and honey. The more viscous honey would demonstrate a greater resistance to flow than the less viscous water. The same principle applies to blood.

The normal temperature of blood is slightly higher than normal body temperature—about 38 °C (or 100.4 °F), compared to 37 °C (or 98.6 °F) for an internal body temperature reading, although daily variations of 0.5 °C are normal. Although the surface of blood vessels is relatively smooth, as blood flows through them, it experiences some friction and resistance, especially as vessels age and lose their elasticity, thereby producing heat. This accounts for its slightly higher temperature.

The pH of blood averages about 7.4; however, it can range from 7.35 to 7.45 in a healthy person. Blood is therefore somewhat more basic (alkaline) on a chemical scale than pure water, which has a pH of 7.0. Blood contains numerous buffers that actually help to regulate pH.

Blood constitutes approximately 8 percent of adult body weight. Adult males typically average about 5 to 6 liters of blood. Females average 4–5 liters.

Blood Plasma

Like other fluids in the body, plasma is composed primarily of water: In fact, it is about 92 percent water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, although many of them are found only in very small quantities.

Note:



Visit this <u>site</u> for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of oxygen in the blood?

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones. The major components of plasma are summarized in [link].

The three major groups of plasma proteins are as follows:

• **Albumin** is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.

- The second most common plasma proteins are the **globulins**. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as an **antibodies** or **immunoglobulins**. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.
- The least abundant plasma protein is **fibrinogen**. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes, such as sodium, potassium, and calcium ions; dissolved gases, such as oxygen, carbon dioxide, and nitrogen; various organic nutrients, such as vitamins, lipids, glucose, and amino acids; and metabolic wastes. All of these nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.

Major Blood Components

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46–63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54–60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35–38 percent	Alpha globulins— liver	Transport, maintain osmotic concentration
			Beta globulins— liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins) —plasma cells	Immune responses
		Fibrinogen 4–7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37–54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils eosinophils basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Note:

Career Connection

Phlebotomy and Medical Lab Technology

Phlebotomists are professionals trained to draw blood (phleb- = "a blood vessel"; -tomy = "to cut"). When more than a few drops of blood are

required, phlebotomists perform a venipuncture, typically of a surface vein in the arm. They perform a capillary stick on a finger, an earlobe, or the heel of an infant when only a small quantity of blood is required. An arterial stick is collected from an artery and used to analyze blood gases. After collection, the blood may be analyzed by medical laboratories or perhaps used for transfusions, donations, or research. While many allied health professionals practice phlebotomy, the American Society of Phlebotomy Technicians issues certificates to individuals passing a national examination, and some large labs and hospitals hire individuals expressively for their skill in phlebotomy.

Medical or clinical laboratories employ a variety of individuals in technical positions:

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor's degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT) typically have an associate's degree but may perform duties similar to those of an MT.
- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

Chapter Review

Blood is a fluid connective tissue critical to the transportation of nutrients, gases, and wastes throughout the body; to defend the body against infection and other threats; and to the homeostatic regulation of pH, temperature, and other internal conditions. Blood is composed of formed elements—erythrocytes, leukocytes, and cell fragments called platelets—and a fluid extracellular matrix called plasma. More than 90 percent of plasma is water.

The remainder is mostly plasma proteins—mainly albumin, globulins, and fibrinogen—and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases. Because of the formed elements and the plasma proteins and other solutes, blood is sticky and more viscous than water. It is also slightly alkaline, and its temperature is slightly higher than normal body temperature.

Glossary

albumin

most abundant plasma protein, accounting for most of the osmotic pressure of plasma

antibodies

(also, immunoglobulins or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

blood

liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system

buffy coat

thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood

fibrinogen

plasma protein produced in the liver and involved in blood clotting

formed elements

cellular components of blood; that is, erythrocytes, leukocytes, and platelets

globulins

heterogeneous group of plasma proteins that includes transport proteins, clotting factors, immune proteins, and others

hematocrit

(also, packed cell volume) volume percentage of erythrocytes in a sample of centrifuged blood

immunoglobulins

(also, antibodies or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

packed cell volume (PCV)

(also, hematocrit) volume percentage of erythrocytes present in a sample of centrifuged blood

plasma

in blood, the liquid extracellular matrix composed mostly of water that circulates the formed elements and dissolved materials throughout the cardiovascular system

platelets

(also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

red blood cells (RBCs)

(also, erythrocytes) one of the formed elements of blood that transports oxygen

white blood cells (WBCs)

(also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

OU Human Physiology: Production of the Formed Elements By the end of this section, you will be able to:

- Trace the generation of the formed elements of blood from bone marrow stem cells
- Discuss the role of hemopoietic growth factors in promoting the production of the formed elements

The lifespan of the formed elements is very brief. Although one type of leukocyte called memory cells can survive for years, most erythrocytes, leukocytes, and platelets normally live only a few hours to a few weeks. Thus, the body must form new blood cells and platelets quickly and continuously. When you donate a unit of blood during a blood drive (approximately 475 mL, or about 1 pint), your body typically replaces the donated plasma within 24 hours, but it takes about 4 to 6 weeks to replace the blood cells. This restricts the frequency with which donors can contribute their blood. The process by which this replacement occurs is called **hemopoiesis**, or hematopoiesis (from the Greek root haima-= "blood"; -poiesis = "production").

Sites of Hemopoiesis

Prior to birth, hemopoiesis occurs in a number of tissues, beginning with the yolk sac of the developing embryo, and continuing in the fetal liver, spleen, lymphatic tissue, and eventually the red bone marrow. Following birth, most hemopoiesis occurs in the red marrow, a connective tissue within the spaces of spongy (cancellous) bone tissue. In children, hemopoiesis can occur in the medullary cavity of long bones; in adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

Throughout adulthood, the liver and spleen maintain their ability to generate the formed elements. This process is referred to as extramedullary hemopoiesis (meaning hemopoiesis outside the medullary cavity of adult bones). When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

Differentiation of Formed Elements from Stem Cells

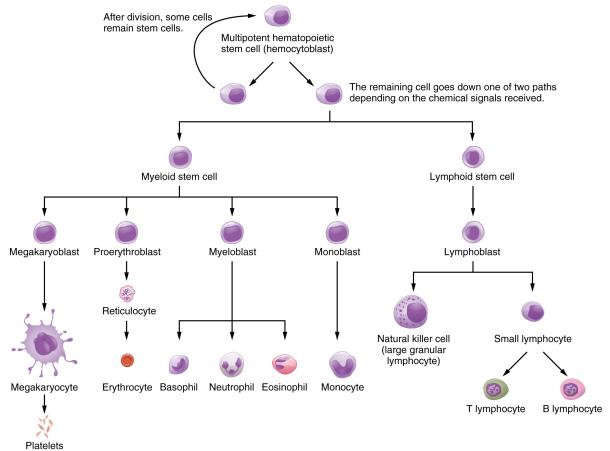
All formed elements arise from stem cells of the red bone marrow. Recall that stem cells undergo mitosis plus cytokinesis (cellular division) to give rise to new daughter cells: One of these remains a stem cell and the other differentiates into one of any number of diverse cell types. Stem cells may be viewed as occupying a hierarchal system, with some loss of the ability to diversify at each step. The totipotent stem cell is the zygote, or fertilized egg. The totipotent (toti- = "all") stem cell gives rise to all cells of the human body. The next level is the pluripotent stem cell, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes. Beneath this level, the mesenchymal cell is a stem cell that develops only into types of connective tissue, including fibrous connective tissue, bone, cartilage, and blood, but not epithelium, muscle, and nervous tissue. One step lower on the hierarchy of stem cells is the **hemopoietic stem cell**, or **hemocytoblast**. All of the formed elements of blood originate from this specific type of cell.

Hemopoiesis begins when the hemopoietic stem cell is exposed to appropriate chemical stimuli collectively called **hemopoietic growth factors**, which prompt it to divide and differentiate. One daughter cell remains a hemopoietic stem cell, allowing hemopoiesis to continue. The other daughter cell becomes either of two types of more specialized stem cells ([link]):

- Lymphoid stem cells give rise to a class of leukocytes known as lymphocytes, which include the various T cells, B cells, and natural killer (NK) cells, all of which function in immunity. However, hemopoiesis of lymphocytes progresses somewhat differently from the process for the other formed elements. In brief, lymphoid stem cells quickly migrate from the bone marrow to lymphatic tissues, including the lymph nodes, spleen, and thymus, where their production and differentiation continues. B cells are so named since they mature in the bone marrow, while T cells mature in the thymus.
- **Myeloid stem cells** give rise to all the other formed elements, including the erythrocytes; megakaryocytes that produce platelets; and

a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes: neutrophils, eosinophils, and basophils.

Hematopoietic System of Bone Marrow



Hemopoiesis is the proliferation and differentiation of the formed elements of blood.

Lymphoid and myeloid stem cells do not immediately divide and differentiate into mature formed elements. As you can see in [link], there are several intermediate stages of precursor cells (literally, forerunner cells), many of which can be recognized by their names, which have the suffix - blast. For instance, megakaryoblasts are the precursors of megakaryocytes, and proerythroblasts become reticulocytes, which eject their nucleus and most other organelles before maturing into erythrocytes.

Hemopoietic Growth Factors

Development from stem cells to precursor cells to mature cells is again initiated by hemopoietic growth factors. These include the following:

- Erythropoietin (EPO) is a glycoprotein hormone secreted by the interstitial fibroblast cells of the kidneys in response to low oxygen levels. It prompts the production of erythrocytes. Some athletes use synthetic EPO as a performance-enhancing drug (called blood doping) to increase RBC counts and subsequently increase oxygen delivery to tissues throughout the body. EPO is a banned substance in most organized sports, but it is also used medically in the treatment of certain anemia, specifically those triggered by certain types of cancer, and other disorders in which increased erythrocyte counts and oxygen levels are desirable.
- **Thrombopoietin**, another glycoprotein hormone, is produced by the liver and kidneys. It triggers the development of megakaryocytes into platelets.
- **Cytokines** are glycoproteins secreted by a wide variety of cells, including red bone marrow, leukocytes, macrophages, fibroblasts, and endothelial cells. They act locally as autocrine or paracrine factors, stimulating the proliferation of progenitor cells and helping to stimulate both nonspecific and specific resistance to disease. There are two major subtypes of cytokines known as colony-stimulating factors and interleukins.
 - Colony-stimulating factors (CSFs) are glycoproteins that act locally, as autocrine or paracrine factors. Some trigger the differentiation of myeloblasts into granular leukocytes, namely, neutrophils, eosinophils, and basophils. These are referred to as granulocyte CSFs. A different CSF induces the production of monocytes, called monocyte CSFs. Both granulocytes and monocytes are stimulated by GM-CSF; granulocytes, monocytes, platelets, and erythrocytes are stimulated by multi-CSF. Synthetic forms of these hormones are often administered to patients with various forms of cancer who are receiving chemotherapy to revive their WBC counts.

• **Interleukins** are another class of cytokine signaling molecules important in hemopoiesis. They were initially thought to be secreted uniquely by leukocytes and to communicate only with other leukocytes, and were named accordingly, but are now known to be produced by a variety of cells including bone marrow and endothelium. Researchers now suspect that interleukins may play other roles in body functioning, including differentiation and maturation of cells, producing immunity and inflammation. To date, more than a dozen interleukins have been identified, with others likely to follow. They are generally numbered IL-1, IL-2, IL-3, etc.

Note:

Everyday Connection **Blood Doping**

In its original intent, the term blood doping was used to describe the practice of injecting by transfusion supplemental RBCs into an individual, typically to enhance performance in a sport. Additional RBCs would deliver more oxygen to the tissues, providing extra aerobic capacity, clinically referred to as VO₂ max. The source of the cells was either from the recipient (autologous) or from a donor with compatible blood (homologous). This practice was aided by the well-developed techniques of harvesting, concentrating, and freezing of the RBCs that could be later thawed and injected, yet still retain their functionality. These practices are considered illegal in virtually all sports and run the risk of infection, significantly increasing the viscosity of the blood and the potential for transmission of blood-borne pathogens if the blood was collected from another individual.

With the development of synthetic EPO in the 1980s, it became possible to provide additional RBCs by artificially stimulating RBC production in the bone marrow. Originally developed to treat patients suffering from anemia, renal failure, or cancer treatment, large quantities of EPO can be generated by recombinant DNA technology. Synthetic EPO is injected under the skin and can increase hematocrit for many weeks. It may also induce polycythemia and raise hematocrit to 70 or greater. This increased

viscosity raises the resistance of the blood and forces the heart to pump more powerfully; in extreme cases, it has resulted in death. Other drugs such as cobalt II chloride have been shown to increase natural EPO gene expression. Blood doping has become problematic in many sports, especially cycling. Lance Armstrong, winner of seven Tour de France and many other cycling titles, was stripped of his victories and admitted to blood doping in 2013.

Note:



Watch this <u>video</u> to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Bone Marrow Sampling and Transplants

Sometimes, a healthcare provider will order a **bone marrow biopsy**, a diagnostic test of a sample of red bone marrow, or a **bone marrow transplant**, a treatment in which a donor's healthy bone marrow—and its stem cells—replaces the faulty bone marrow of a patient. These tests and procedures are often used to assist in the diagnosis and treatment of various severe forms of anemia, such as thalassemia major and sickle cell anemia, as well as some types of cancer, specifically leukemia.

In the past, when a bone marrow sample or transplant was necessary, the procedure would have required inserting a large-bore needle into the region near the iliac crest of the pelvic bones (os coxae). This location was preferred, since its location close to the body surface makes it more

accessible, and it is relatively isolated from most vital organs. Unfortunately, the procedure is quite painful.

Now, direct sampling of bone marrow can often be avoided. In many cases, stem cells can be isolated in just a few hours from a sample of a patient's blood. The isolated stem cells are then grown in culture using the appropriate hemopoietic growth factors, and analyzed or sometimes frozen for later use.

For an individual requiring a transplant, a matching donor is essential to prevent the immune system from destroying the donor cells—a phenomenon known as tissue rejection. To treat patients with bone marrow transplants, it is first necessary to destroy the patient's own diseased marrow through radiation and/or chemotherapy. Donor bone marrow stem cells are then intravenously infused. From the bloodstream, they establish themselves in the recipient's bone marrow.

Chapter Review

Through the process of hemopoiesis, the formed elements of blood are continually produced, replacing the relatively short-lived erythrocytes, leukocytes, and platelets. Hemopoiesis begins in the red bone marrow, with hemopoietic stem cells that differentiate into myeloid and lymphoid lineages. Myeloid stem cells give rise to most of the formed elements. Lymphoid stem cells give rise only to the various lymphocytes designated as B and T cells, and NK cells. Hemopoietic growth factors, including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins, promote the proliferation and differentiation of formed elements.

Glossary

bone marrow biopsy diagnostic test of a sample of red bone marrow

bone marrow transplant

treatment in which a donor's healthy bone marrow with its stem cells replaces diseased or damaged bone marrow of a patient

colony-stimulating factors (CSFs)

glycoproteins that trigger the proliferation and differentiation of myeloblasts into granular leukocytes (basophils, neutrophils, and eosinophils)

cytokines

class of proteins that act as autocrine or paracrine signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease

erythropoietin (EPO)

glycoprotein that triggers the bone marrow to produce RBCs; secreted by the kidney in response to low oxygen levels

hemocytoblast

hemopoietic stem cell that gives rise to the formed elements of blood

hemopoiesis

production of the formed elements of blood

hemopoietic growth factors

chemical signals including erythropoietin, thrombopoietin, colonystimulating factors, and interleukins that regulate the differentiation and proliferation of particular blood progenitor cells

hemopoietic stem cell

type of pluripotent stem cell that gives rise to the formed elements of blood (hemocytoblast)

interleukins

signaling molecules that may function in hemopoiesis, inflammation, and specific immune responses

lymphoid stem cells

type of hemopoietic stem cells that gives rise to lymphocytes, including various T cells, B cells, and NK cells, all of which function in immunity

myeloid stem cells

type of hemopoietic stem cell that gives rise to some formed elements, including erythrocytes, megakaryocytes that produce platelets, and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes (neutrophils, eosinophils, and basophils)

thrombopoietin

hormone secreted by the liver and kidneys that prompts the development of megakaryocytes into thrombocytes (platelets)

OU Human Physiology: Erythrocytes By the end of this section, you will be able to:

- Describe the anatomy and function of erythrocytes
- Explain the steps in erythropoiesis
- Explain why RBCs cannot undergo cell division and the mechanism for destroying worn out RBC
- Explain the composition and function of hemoglobin
- Determine the cause of several blood disorders and discuss whether or not those disorders are reversible

The **erythrocyte**, commonly known as a red blood cell (or RBC), is by far the most common formed element: A single drop of blood contains millions of erythrocytes and just thousands of leukocytes. Specifically, males have about 5.4 million erythrocytes per microliter (μ L) of blood, and females have approximately 4.8 million per μ L. In fact, erythrocytes are estimated to make up about 25 percent of the total cells in the body. As you can imagine, they are quite small cells, with a mean diameter of only about 7–8 micrometers (μ m) ([link]). The primary functions of erythrocytes are to pick up inhaled oxygen from the lungs and transport it to the body's tissues, and to pick up some (about 24 percent) carbon dioxide waste at the tissues and transport it to the lungs for exhalation. Erythrocytes remain within the vascular network. Although leukocytes typically leave the blood vessels to perform their defensive functions, movement of erythrocytes from the blood vessels is abnormal.

Summary of Formed Elements in Blood

Formed element	Major subtypes	Numbers present per microliter (<i>µ</i> L) and mean (range)	Appearance in a standard blood smear	Summary of functions	Comments
Erythrocytes (red blood cells)			Flattened biconcave disk; no nucleus; pale red color	Transport oxygen and some carbon dioxide between tissues and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)		7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes including neutrophils, eosinophils, and basophils	4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils		Nuclear lobes increase with age:	Phagocytic; particularly effective	Most common leukocyte:

			pale lilac granules	against bacteria. Release cytotoxic chemicals from granules	lifespan of minutes to days
	Eosinophils	165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen- antibody complexes. Release antihistamines. Increase in allergies and parasitic infections	Lifespan of minutes to days
	Basophils	44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Promotes inflammation	Least common leukocyte; lifespan unknown
	Agranulocytes including lymphocytes and monocytes	2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple- shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes	2185 (1500–4000)	Spherical cells with a single often large nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes	455 (200–950)	Largest leukocyte with an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system	Produced in red bone marrow; referred to as macrophages after leaving circulation
Platelets	XI.	350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; purple stain	Hemostasis plus release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

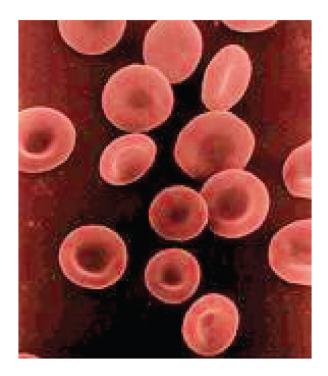
Shape and Structure of Erythrocytes

As an erythrocyte matures in the red bone marrow, it extrudes its nucleus and most of its other organelles. During the first day or two that it is in the circulation, an immature erythrocyte, known as a **reticulocyte**, will still typically contain remnants of organelles. Reticulocytes should comprise approximately 1–2 percent of the erythrocyte count and provide a rough estimate of the rate of RBC production, with abnormally low or high rates indicating deviations in the production of these cells. These remnants, primarily of networks (reticulum) of ribosomes, are quickly shed, however,

and mature, circulating erythrocytes have few internal cellular structural components. Lacking mitochondria, for example, they rely on anaerobic respiration. This means that they do not utilize any of the oxygen they are transporting, so they can deliver it all to the tissues. They also lack endoplasmic reticula and do not synthesize proteins. Erythrocytes do, however, contain some structural proteins that help the blood cells maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

Erythrocytes are biconcave disks; that is, they are plump at their periphery and very thin in the center ([link]). Since they lack most organelles, there is more interior space for the presence of the hemoglobin molecules that, as you will see shortly, transport gases. The biconcave shape also provides a greater surface area across which gas exchange can occur, relative to its volume; a sphere of a similar diameter would have a lower surface area-tovolume ratio. In the capillaries, the oxygen carried by the erythrocytes can diffuse into the plasma and then through the capillary walls to reach the cells, whereas some of the carbon dioxide produced by the cells as a waste product diffuses into the capillaries to be picked up by the erythrocytes. Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur. However, the space within capillaries can be so minute that, despite their own small size, erythrocytes may have to fold in on themselves if they are to make their way through. Fortunately, their structural proteins like spectrin are flexible, allowing them to bend over themselves to a surprising degree, then spring back again when they enter a wider vessel. In wider vessels, erythrocytes may stack up much like a roll of coins, forming a rouleaux, from the French word for "roll."

Shape of Red Blood Cells

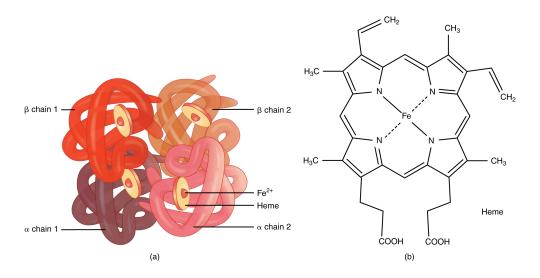


Erythrocytes are biconcave discs with very shallow centers. This shape optimizes the ratio of surface area to volume, facilitating gas exchange. It also enables them to fold up as they move through narrow blood vessels.

Hemoglobin

Hemoglobin is a large molecule made up of proteins and iron. It consists of four folded chains of a protein called **globin**, designated alpha 1 and 2, and beta 1 and 2 ([link]a). Each of these globin molecules is bound to a red pigment molecule called **heme**, which contains an ion of iron (Fe²⁺) ([link]b).

Hemoglobin



(a) A molecule of hemoglobin contains four globin proteins, each of which is bound to one molecule of the iron-containing pigment heme. (b) A single erythrocyte can contain 300 million hemoglobin molecules, and thus more than 1 billion oxygen molecules.

Each iron ion in the heme can bind to one oxygen molecule; therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and therefore can bind to and transport up to 1.2 billion oxygen molecules (see [link]b).

In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming **oxyhemoglobin**. The bright red, oxygenated hemoglobin travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red **deoxyhemoglobin**, sometimes referred to as reduced hemoglobin. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely if ever leaves all of its oxygen behind. In the capillaries, carbon dioxide enters the bloodstream. About 76 percent dissolves in the plasma, some of it remaining as dissolved CO₂, and the remainder forming bicarbonate ion. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as **carbaminohemoglobin**. From the capillaries, the hemoglobin carries

carbon dioxide back to the lungs, where it releases it for exchange of oxygen.

Changes in the levels of RBCs can have significant effects on the body's ability to effectively deliver oxygen to the tissues. Ineffective hematopoiesis results in insufficient numbers of RBCs and results in one of several forms of anemia. An overproduction of RBCs produces a condition called polycythemia. The primary drawback with polycythemia is not a failure to directly deliver enough oxygen to the tissues, but rather the increased viscosity of the blood, which makes it more difficult for the heart to circulate the blood.

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen, resulting in another form of anemia. In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of hemoglobin sites occupied by oxygen in a patient's blood. Clinically this value is commonly referred to simply as "percent sat."

Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient's finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect **hypoxemia**, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply pO_2 and is typically recorded in units of millimeters of mercury, mm Hg.

The kidneys filter about 180 liters (~380 pints) of blood in an average adult each day, or about 20 percent of the total resting volume, and thus serve as ideal sites for receptors that determine oxygen saturation. In response to

hypoxemia, less oxygen will exit the vessels supplying the kidney, resulting in hypoxia (low oxygen concentration) in the tissue fluid of the kidney where oxygen concentration is actually monitored. Interstitial fibroblasts within the kidney secrete EPO, thereby increasing erythrocyte production and restoring oxygen levels. In a classic negative-feedback loop, as oxygen saturation rises, EPO secretion falls, and vice versa, thereby maintaining homeostasis. Populations dwelling at high elevations, with inherently lower levels of oxygen in the atmosphere, naturally maintain a hematocrit higher than people living at sea level. Consequently, people traveling to high elevations may experience symptoms of hypoxemia, such as fatigue, headache, and shortness of breath, for a few days after their arrival. In response to the hypoxemia, the kidneys secrete EPO to step up the production of erythrocytes until homeostasis is achieved once again. To avoid the symptoms of hypoxemia, or altitude sickness, mountain climbers typically rest for several days to a week or more at a series of camps situated at increasing elevations to allow EPO levels and, consequently, erythrocyte counts to rise. When climbing the tallest peaks, such as Mt. Everest and K2 in the Himalayas, many mountain climbers rely upon bottled oxygen as they near the summit.

Lifecycle of Erythrocytes

Production of erythrocytes in the marrow occurs at the staggering rate of more than 2 million cells per second. For this production to occur, a number of raw materials must be present in adequate amounts. These include the same nutrients that are essential to the production and maintenance of any cell, such as glucose, lipids, and amino acids. However, erythrocyte production also requires several trace elements:

• Iron. We have said that each heme group in a hemoglobin molecule contains an ion of the trace mineral iron. On average, less than 20 percent of the iron we consume is absorbed. Heme iron, from animal foods such as meat, poultry, and fish, is absorbed more efficiently than non-heme iron from plant foods. Upon absorption, iron becomes part of the body's total iron pool. The bone marrow, liver, and spleen can store iron in the protein compounds **ferritin** and hemosiderin. Ferroportin transports the iron across the intestinal cell plasma

- membranes and from its storage sites into tissue fluid where it enters the blood. When EPO stimulates the production of erythrocytes, iron is released from storage, bound to transferrin, and carried to the red marrow where it attaches to erythrocyte precursors.
- Copper. A trace mineral, copper is a component of two plasma proteins, hephaestin and ceruloplasmin. Without these, hemoglobin could not be adequately produced. Located in intestinal villi, hephaestin enables iron to be absorbed by intestinal cells. Ceruloplasmin transports copper. Both enable the oxidation of iron from Fe²⁺ to Fe³⁺, a form in which it can be bound to its transport protein, **transferrin**, for transport to body cells. In a state of copper deficiency, the transport of iron for heme synthesis decreases, and iron can accumulate in tissues, where it can eventually lead to organ damage.
- Zinc. The trace mineral zinc functions as a co-enzyme that facilitates the synthesis of the heme portion of hemoglobin.
- B vitamins. The B vitamins folate and vitamin B₁₂ function as coenzymes that facilitate DNA synthesis. Thus, both are critical for the synthesis of new cells, including erythrocytes.

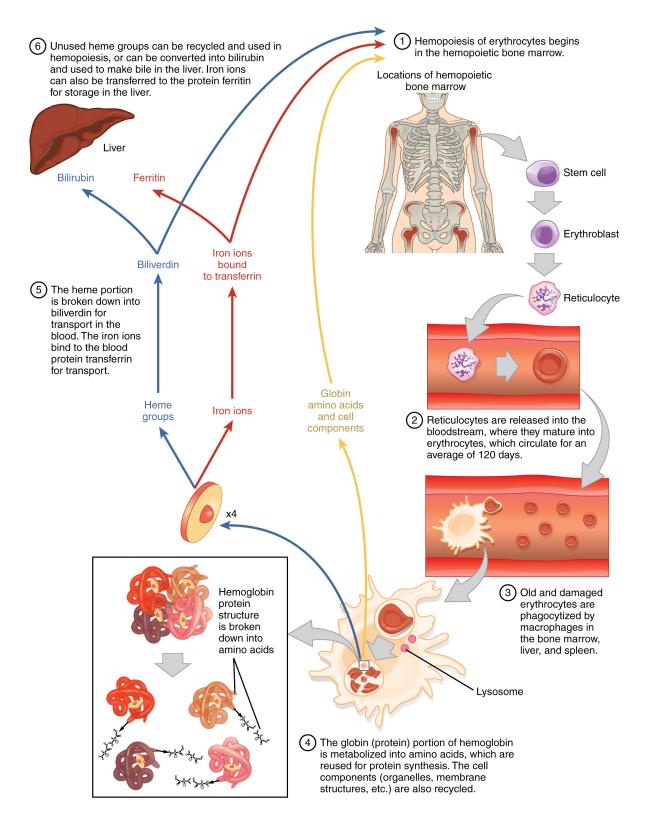
Erythrocytes live up to 120 days in the circulation, after which the worn-out cells are degraded. The spleen is primarily responsible for destroying old red blood cells; however the liver also plays a role in their destruction. Both the liver and spleen house **macrophages** that will engulf worn-out red blood cells. The components of the degraded erythrocytes' hemoglobin are then processed as follows:

- Globin, the protein portion of hemoglobin, is broken down into amino acids, which can be sent back to the bone marrow to be used in the production of new erythrocytes. Hemoglobin that is not phagocytized is broken down in the circulation, releasing alpha and beta chains that are removed from circulation by the kidneys.
- The iron contained in the heme portion of hemoglobin may be stored in the liver or spleen, primarily in the form of ferritin or hemosiderin, or carried through the bloodstream by transferrin to the red bone marrow for recycling into new erythrocytes.

• The non-iron portion of heme is degraded into the waste product biliverdin, a green pigment, and then into another waste product, bilirubin, a yellow pigment. Bilirubin binds to albumin and travels in the blood to the liver, which uses it in the manufacture of bile, a compound released into the intestines to help emulsify dietary fats. In the large intestine, bacteria breaks the bilirubin apart from the bile and converts it to urobilinogen and then into stercobilin. It is then eliminated from the body in the feces. Broad-spectrum antibiotics typically eliminate these bacteria as well and may alter the color of feces. The kidneys also remove any circulating bilirubin and other related metabolic byproducts such as urobilins and secrete them into the urine.

The breakdown pigments formed from the destruction of hemoglobin can be seen in a variety of situations. At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colors associated with bruising. With a failing liver, bilirubin cannot be removed effectively from circulation and causes the body to assume a yellowish tinge associated with jaundice. Stercobilins within the feces produce the typical brown color associated with this waste. And the yellow of urine is associated with the urobilins.

The erythrocyte lifecycle is summarized in [link]. Erythrocyte Lifecycle



Erythrocytes are produced in the bone marrow and sent into the circulation. At the end of their lifecycle, they are destroyed by

Disorders of Erythrocytes

The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person's health. When oxygen carrying capacity is low, the general condition is called **anemia**. There are a number of causes for anemia but is generally associated with a decrease in the number of erythrocytes or a decrease in the size of erythrocytes. There are more than 400 types of anemia and more than 3.5 million Americans suffer from this condition. Anemia can be broken down into three major groups: those caused by blood loss, those caused by faulty or decreased RBC production, and those caused by excessive destruction of RBCs. Clinicians often use two groupings in diagnosis: The kinetic approach focuses on evaluating the production, destruction, and removal of RBCs, whereas the morphological approach examines the RBCs themselves, paying particular emphasis to their size. A common test is the mean corpuscle volume (MCV), which measures size. Normal-sized cells are referred to as normocytic, smaller-than-normal cells are referred to as microcytic, and larger-than-normal cells are referred to as macrocytic. Reticulocyte counts are also important and may reveal inadequate production of RBCs. The effects of the various anemias are widespread, because reduced numbers of RBCs or hemoglobin will result in lower levels of oxygen being delivered to body tissues. Since oxygen is required for tissue functioning, anemia produces fatigue, lethargy, and an increased risk for infection. An oxygen deficit in the brain impairs the ability to think clearly, and may prompt headaches and irritability. Lack of oxygen leaves the patient short of breath, even as the heart and lungs work harder in response to the deficit.

Blood loss anemias are fairly straightforward. In addition to bleeding from wounds or other lesions, these forms of anemia may be due to ulcers, hemorrhoids, inflammation of the stomach (gastritis), and some cancers of the gastrointestinal tract. The excessive use of aspirin or other nonsteroidal anti-inflammatory drugs such as ibuprofen can trigger ulceration and

gastritis. Excessive menstruation and loss of blood during childbirth are also potential causes.

Anemias caused by faulty or decreased RBC production include sickle cell anemia, iron deficiency anemia, vitamin deficiency anemia, and diseases of the bone marrow and stem cells.

• A characteristic change in the shape of erythrocytes is seen in **sickle cell disease** (also referred to as sickle cell anemia). A genetic disorder, it is caused by production of an abnormal type of hemoglobin, called hemoglobin S, which delivers less oxygen to tissues and causes erythrocytes to assume a sickle (or crescent) shape, especially at low oxygen concentrations ([link]). These abnormally shaped cells can then become lodged in narrow capillaries because they are unable to fold in on themselves to squeeze through, blocking blood flow to tissues and causing a variety of serious problems from painful joints to delayed growth and even blindness and cerebrovascular accidents (strokes). Sickle cells can also result in hemolysis (hemolytic anemia) —rupture of an excessive number of erythrocytes. Sickle cell anemia is a genetic condition particularly found in individuals of African descent.

Sickle Cells



Sickle cell anemia is caused by a mutation in one of the hemoglobin genes. Erythrocytes produce an abnormal type of hemoglobin, which causes the cell to take on a sickle or crescent shape. (credit: Janice Haney Carr)

- Iron deficiency anemia is the most common type and results when the
 amount of available iron is insufficient to allow production of
 sufficient heme. This condition can occur in individuals with a
 deficiency of iron in the diet and is especially common in teens and
 children as well as in vegans and vegetarians. Additionally, iron
 deficiency anemia may be caused by either an inability to absorb and
 transport iron or slow, chronic bleeding.
- Vitamin-deficient anemias generally involve insufficient vitamin B12 and folate.
 - Megaloblastic anemia involves a deficiency of vitamin B12 and/or folate, and often involves diets deficient in these essential nutrients. Lack of meat or a viable alternate source, and overcooking or eating insufficient amounts of vegetables may lead to a lack of folate.
 - Pernicious anemia is caused by poor absorption of vitamin B12 and is often seen in patients with Crohn's disease (a severe intestinal disorder often treated by surgery), surgical removal of the intestines or stomach (common in some weight loss surgeries), intestinal parasites, and AIDS.
 - Pregnancies, some medications, excessive alcohol consumption, and some diseases such as celiac disease are also associated with vitamin deficiencies. It is essential to provide sufficient folic acid during the early stages of pregnancy to reduce the risk of

neurological defects, including spina bifida, a failure of the neural tube to close.

- Assorted disease processes can also interfere with the production and formation of RBCs and hemoglobin. If myeloid stem cells are defective or replaced by cancer cells, there will be insufficient quantities of RBCs produced.
 - Aplastic anemia is the condition in which there are deficient numbers of RBC stem cells. Aplastic anemia is often inherited, or it may be triggered by radiation, medication, chemotherapy, or infection.
 - Thalassemia is an inherited condition typically occurring in individuals from the Middle East, the Mediterranean, African, and Southeast Asia, in which maturation of the RBCs does not proceed normally. The most severe form is called Cooley's anemia.
 - Lead exposure from industrial sources or even dust from paint chips of iron-containing paints or pottery that has not been properly glazed may also lead to destruction of the red marrow.
- Various disease processes also can lead to anemias. These include chronic kidney diseases often associated with a decreased production of EPO, hypothyroidism, some forms of cancer, lupus, and rheumatoid arthritis.

In contrast to anemia, an elevated RBC count is called **polycythemia** and is detected in a patient's elevated hematocrit. It can occur transiently in a person who is dehydrated; when water intake is inadequate or water losses are excessive, the plasma volume falls. As a result, the hematocrit rises. For reasons mentioned earlier, a mild form of polycythemia is chronic but normal in people living at high altitudes. Some elite athletes train at high elevations specifically to induce this phenomenon. Finally, a type of bone marrow disease called polycythemia vera (from the Greek vera = "true") causes an excessive production of immature erythrocytes. Polycythemia vera can dangerously elevate the viscosity of blood, raising blood pressure and making it more difficult for the heart to pump blood throughout the body. It is a relatively rare disease that occurs more often in men than

women, and is more likely to be present in elderly patients those over 60 years of age.

Chapter Review

The most abundant formed elements in blood, erythrocytes are red, biconcave disks packed with an oxygen-carrying compound called hemoglobin. The hemoglobin molecule contains four globin proteins bound to a pigment molecule called heme, which contains an ion of iron. In the bloodstream, iron picks up oxygen in the lungs and drops it off in the tissues; the amino acids in hemoglobin then transport carbon dioxide from the tissues back to the lungs. Erythrocytes live only 120 days on average, and thus must be continually replaced. Worn-out erythrocytes are phagocytized by macrophages and their hemoglobin is broken down. The breakdown products are recycled or removed as wastes: Globin is broken down into amino acids for synthesis of new proteins; iron is stored in the liver or spleen or used by the bone marrow for production of new erythrocytes; and the remnants of heme are converted into bilirubin, or other waste products that are taken up by the liver and excreted in the bile or removed by the kidneys. Anemia is a deficiency of RBCs or hemoglobin, whereas polycythemia is an excess of RBCs.

Glossary

anemia

deficiency of red blood cells or hemoglobin

bilirubin

yellowish bile pigment produced when iron is removed from heme and is further broken down into waste products

biliverdin

green bile pigment produced when the non-iron portion of heme is degraded into a waste product; converted to bilirubin in the liver

carbaminohemoglobin

compound of carbon dioxide and hemoglobin, and one of the ways in which carbon dioxide is carried in the blood

deoxyhemoglobin

molecule of hemoglobin without an oxygen molecule bound to it

erythrocyte

(also, red blood cell) mature myeloid blood cell that is composed mostly of hemoglobin and functions primarily in the transportation of oxygen and carbon dioxide

ferritin

protein-containing storage form of iron found in the bone marrow, liver, and spleen

globin

heme-containing globular protein that is a constituent of hemoglobin

heme

red, iron-containing pigment to which oxygen binds in hemoglobin

hemoglobin

oxygen-carrying compound in erythrocytes

hypoxemia

below-normal level of oxygen saturation of blood (typically <95 percent)

macrophage

phagocytic cell of the myeloid lineage; a matured monocyte

oxyhemoglobin

molecule of hemoglobin to which oxygen is bound

polycythemia

elevated level of hemoglobin, whether adaptive or pathological

reticulocyte

immature erythrocyte that may still contain fragments of organelles

sickle cell disease

(also, sickle cell anemia) inherited blood disorder in which hemoglobin molecules are malformed, leading to the breakdown of RBCs that take on a characteristic sickle shape

thalassemia

inherited blood disorder in which maturation of RBCs does not proceed normally, leading to abnormal formation of hemoglobin and the destruction of RBCs

transferrin

plasma protein that binds reversibly to iron and distributes it throughout the body

OU Human Physiology: Leukocytes and Platelets By the end of this section, you will be able to:

- Describe the general characteristics of leukocytes including their generalized function
- Classify leukocytes according to their lineage, their main structural features, and their primary functions
- Categorize the various leukocytes as either granulocytes or agranulocytes
- Explain the function for each of the leukocytes and when these leukocytes may be abnormally high
- Compare and contrast leukopenia to leukocytosis
- Identify the lineage, basic structure and function of platelets
- Explain why platelets are not cells
- Compare and contrast thrombocytopenia to thrombocytosis

The **leukocyte**, commonly known as a white blood cell (or WBC), is a major component of the body's defenses against disease. Leukocytes protect the body against invading microorganisms and body cells with mutated DNA, and they clean up debris. Platelets are essential for the repair of blood vessels when damage to them has occurred; they also provide growth factors for healing and repair. See [link] for a summary of leukocytes and platelets.

Characteristics of Leukocytes

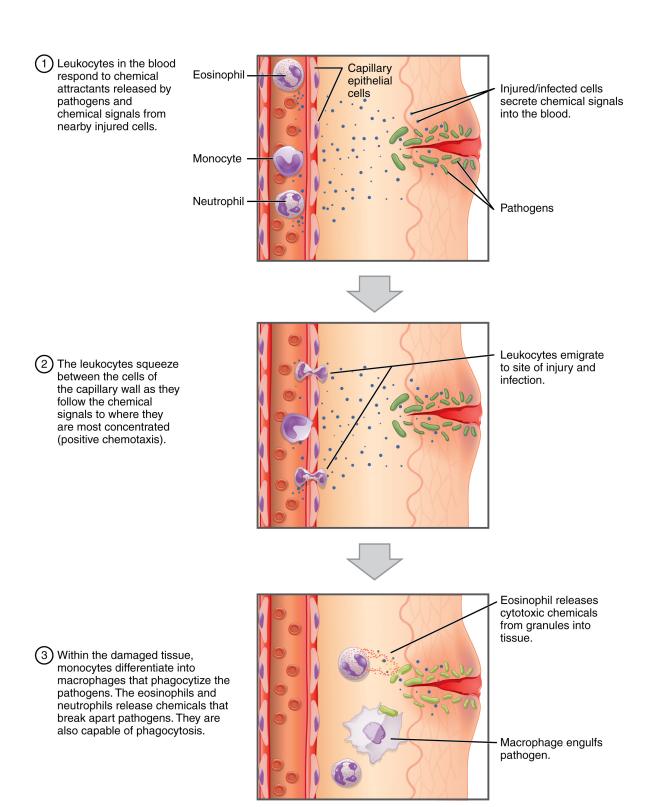
Although leukocytes and erythrocytes both originate from hematopoietic stem cells in the bone marrow, they are very different from each other in many significant ways. For instance, leukocytes are far less numerous than erythrocytes: Typically there are only 5000 to 10,000 per μ L. They are also larger than erythrocytes and are the only formed elements that are complete cells, possessing a nucleus and organelles. And although there is just one type of erythrocyte, there are many types of leukocytes. Most of these types have a much shorter lifespan than that of erythrocytes, some as short as a few hours or even a few minutes in the case of acute infection.

Mature leukocytes are derived from one of two stem cells; myeloid stem cells or lymphoid stem cells. Myeloid stem cells will ultimately give rise to basophils, neutrophils, eosinophils, and monocytes; whereas lymphoid stem cells will give rise to lymphocytes.

One of the most distinctive characteristics of leukocytes is their movement. Whereas erythrocytes spend their days circulating within the blood vessels, leukocytes routinely leave the bloodstream to perform their defensive functions in the body's tissues. For leukocytes, the vascular network is simply a highway they travel and soon exit to reach their true destination. When they arrive, they are often given distinct names, such as macrophage or microglia, depending on their function. As shown in [link], they leave the capillaries—the smallest blood vessels—or other small vessels through a process known as **emigration** (from the Latin for "removal") or **diapedesis** (dia- = "through"; -pedan = "to leap") in which they squeeze through adjacent cells in a blood vessel wall.

Once they have exited the capillaries, some leukocytes will take up fixed positions in lymphatic tissue, bone marrow, the spleen, the thymus, or other organs. Others will move about through the tissue spaces very much like amoebas, continuously extending their plasma membranes, sometimes wandering freely, and sometimes moving toward the direction in which they are drawn by chemical signals. This attracting of leukocytes occurs because of **positive chemotaxis** (literally "movement in response to chemicals"), a phenomenon in which injured or infected cells and nearby leukocytes emit the equivalent of a chemical "911" call, attracting more leukocytes to the site. In clinical medicine, the differential counts of the types and percentages of leukocytes present are often key indicators in making a diagnosis and selecting a treatment.

Emigration



Leukocytes exit the blood vessel and then move through the connective tissue of the dermis toward the site of a wound. Some leukocytes, such as the eosinophil and neutrophil, are characterized as granular leukocytes. They release chemicals from their granules that destroy pathogens; they are also capable of phagocytosis. The monocyte, an agranular leukocyte, differentiates into a macrophage that then phagocytizes the pathogens.

Classification of Leukocytes

When scientists first began to observe stained blood slides, it quickly became evident that leukocytes could be divided into two groups, according to whether their cytoplasm contained highly visible granules:

- **Granular leukocytes** contain abundant granules within the cytoplasm. They include neutrophils, eosinophils, and basophils (you can view their lineage from myeloid stem cells in [link]).
- While granules are not totally lacking in **agranular leukocytes**, they are far fewer and less obvious. Agranular leukocytes include monocytes, which mature into macrophages that are phagocytic, and lymphocytes, which arise from the lymphoid stem cell line.

Granular Leukocytes

We will consider the granular leukocytes in order from most common to least common. All of these are produced in the red bone marrow and have a short lifespan of hours to days. They typically have a lobed nucleus that is often referred to as polymorphonuclear (a nucleus with many forms) or multilobed due to their many-lobed nuclei and are classified according to which type of stain best highlights their granules ([link]).

Granular Leukocytes







Eosinophil



Basophil

A neutrophil has small granules that stain light lilac and a nucleus with two to five lobes. An eosinophil's granules are slightly larger and stain reddish-orange, and its nucleus has two to three lobes. A basophil has large granules that stain dark blue to purple and a two-lobed nucleus.

The most common of all the leukocytes, **neutrophils** will normally comprise 50–70 percent of total leukocyte count. They are 10– $12~\mu m$ in diameter, significantly larger than erythrocytes. They are called neutrophils because their granules show up most clearly with stains that are chemically neutral (neither acidic nor basic). The granules are numerous but quite fine and normally appear light lilac. The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell. Older neutrophils have increasing numbers of lobes and are often referred to as **polymorphonuclear** (a nucleus with many forms), or simply "polys."

Neutrophils are rapid responders to the site of infection and are efficient phagocytes with a preference for bacteria. Their granules include **lysozyme**, an enzyme capable of lysing, or breaking down, bacterial cell walls; oxidants such as hydrogen peroxide; and **defensins**, proteins that bind to and puncture bacterial and fungal plasma membranes, so that the cell contents leak out. Abnormally high counts of neutrophils indicate infection and/or inflammation, particularly triggered by bacteria, but are also found in burn patients and others experiencing unusual stress. A burn injury increases the proliferation of neutrophils in order to fight off infection that can result from the destruction of the barrier of the skin. Low counts may be caused by drug toxicity and other disorders, and may increase an individual's susceptibility to infection.

Eosinophils typically represent 2–4 percent of total leukocyte count. They are also 10– $12~\mu m$ in diameter. The granules of eosinophils stain best with an acidic stain known as eosin. The nucleus of the eosinophil will typically

have two to three lobes and, if stained properly, the granules will have a distinct red to orange color.

The granules of eosinophils include antihistamine molecules, which counteract the activities of histamines, inflammatory chemicals produced by basophils and mast cells. Some eosinophil granules contain molecules toxic to parasitic worms, which can enter the body through the integument, or when an individual consumes raw or undercooked fish or meat. Eosinophils are also capable of phagocytosis and are particularly effective when antibodies bind to the target and form an antigen-antibody complex. High counts of eosinophils are typical of patients experiencing allergies, parasitic worm infestations, and some autoimmune diseases. Low counts may be due to drug toxicity and stress.

Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They are slightly smaller than neutrophils and eosinophils at 8–10 μ m in diameter. The granules of basophils stain best with basic (alkaline) stains. Basophils contain large granules that pick up a dark blue stain and are so common they may make it difficult to see the two-lobed nucleus.

In general, basophils intensify the inflammatory response. They share this trait with mast cells. In the past, mast cells were considered to be basophils that left the circulation. However, this appears not to be the case, as the two cell types develop from different lineages.

The granules of basophils release histamines, which contribute to inflammation, and heparin, which opposes blood clotting. High counts of basophils are associated with allergies, parasitic infections, and hypothyroidism. Low counts are associated with pregnancy, stress, and hyperthyroidism.

Agranular Leukocytes

Agranular leukocytes contain smaller, less-visible granules in their cytoplasm than do granular leukocytes. The nucleus is mononuclear and

therefore lacks lobes. There are two major types of agranulocytes: lymphocytes and monocytes (see [link]).

Lymphocytes are the only formed element of blood that arises from lymphoid stem cells. Although they form initially in the bone marrow, much of their subsequent development and reproduction occurs in the lymphatic tissues. Lymphocytes are the second most common type of leukocyte, accounting for about 20–30 percent of all leukocytes, and are essential for the immune response. The size range of lymphocytes is quite extensive, with some authorities recognizing two size classes and others three. Typically, the large cells are $10-14~\mu m$ and have a smaller nucleus-to-cytoplasm ratio and more granules. The smaller cells are typically 6–9 μm with a larger volume of nucleus to cytoplasm, creating a "halo" effect. A few cells may fall outside these ranges, at $14-17~\mu m$. This finding has led to the three size range classification.

The three major groups of lymphocytes include natural killer cells, B cells, and T cells. **Natural killer (NK) cells** are capable of recognizing cells that do not express "self" proteins on their plasma membrane or that contain foreign or abnormal markers. These "nonself" cells include cancer cells, cells infected with a virus, and other cells with atypical surface proteins. Thus, they provide generalized, nonspecific immunity. The larger lymphocytes are typically NK cells.

B cells and T cells, also called **B lymphocytes** and **T lymphocytes**, play prominent roles in defending the body against specific pathogens (disease-causing microorganisms) and are involved in specific immunity. One form of B cells (plasma cells) produces the antibodies or immunoglobulins that bind to specific foreign or abnormal components of plasma membranes. This is also referred to as humoral (body fluid) immunity. T cells provide cellular-level immunity by physically attacking foreign or diseased cells. A **memory cell** is a variety of both B and T cells that forms after exposure to a pathogen and mounts rapid responses upon subsequent exposures. Unlike other leukocytes, memory cells live for many years. B cells undergo a maturation process in the <u>b</u>one marrow, whereas T cells undergo maturation in the <u>t</u>hymus. This site of the maturation process gives rise to the name B and T cells. The functions of lymphocytes are complex and will be covered

in detail in the chapter covering the lymphatic system and immunity. Smaller lymphocytes are either B or T cells, although they cannot be differentiated in a normal blood smear.

Abnormally high lymphocyte counts are characteristic of viral infections as well as some types of cancer. Abnormally low lymphocyte counts are characteristic of prolonged (chronic) illness or immunosuppression, including that caused by HIV infection and drug therapies that often involve steroids.

Monocytes originate from myeloid stem cells. They normally represent 2–8 percent of the total leukocyte count. They are typically easily recognized by their large size of $12–20~\mu m$ and indented or horseshoe-shaped nuclei. Macrophages are monocytes that have left the circulation and invaded the tissues. These macrophages phagocytize debris, foreign pathogens, wornout erythrocytes, and many other dead, worn out, or damaged cells. Macrophages also release antimicrobial defensins and chemotactic chemicals that attract other leukocytes to the site of an infection. Some macrophages occupy fixed locations, whereas others wander through the tissue fluid.

Abnormally high counts of monocytes are associated with viral or fungal infections, tuberculosis, and some forms of leukemia and other chronic diseases. Abnormally low counts are typically caused by suppression of the bone marrow.

Lifecycle of Leukocytes

Most leukocytes have a relatively short lifespan, typically measured in hours or days. Production of all leukocytes begins in the bone marrow under the influence of CSFs and interleukins. Secondary production and maturation of lymphocytes occurs in specific regions of lymphatic tissue known as germinal centers. Lymphocytes are fully capable of mitosis and may produce clones of cells with identical properties. This capacity enables an individual to maintain immunity throughout life to many threats that have been encountered in the past.

Disorders of Leukocytes

Leukopenia is a condition in which too few leukocytes are produced. If this condition is pronounced, the individual may be unable to ward off disease. Excessive leukocyte proliferation is known as **leukocytosis**. Although leukocyte counts are high, the cells themselves are often nonfunctional, leaving the individual at increased risk for disease.

Leukemia is a cancer involving an abundance of leukocytes. It may involve only one specific type of leukocyte from either the myeloid line (myelocytic leukemia) or the lymphoid line (lymphocytic leukemia). In chronic leukemia, mature leukocytes accumulate and fail to die. In acute leukemia, there is an overproduction of young, immature leukocytes. In both conditions the cells do not function properly.

Lymphoma is a form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues. As in leukemia, the malignant leukocytes do not function properly, and the patient is vulnerable to infection. Some forms of lymphoma tend to progress slowly and respond well to treatment. Others tend to progress quickly and require aggressive treatment, without which they are rapidly fatal.

Platelets

You may occasionally see platelets referred to as **thrombocytes**, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a **megakaryocyte** that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see [link]) and are large, typically $50-100~\mu m$ in diameter, and contain an enlarged, lobed nucleus. As noted earlier, thrombopoietin, a glycoprotein secreted by the kidneys and liver, stimulates the proliferation of megakaryoblasts, which mature into megakaryocytes. These remain within bone marrow tissue ([link]) and ultimately form platelet-precursor extensions that extend through the walls of bone marrow capillaries to release into the circulation thousands of cytoplasmic fragments, each enclosed by a bit of plasma membrane. These

enclosed fragments are platelets. Each megakarocyte releases 2000–3000 platelets during its lifespan. Following platelet release, megakaryocyte remnants, which are little more than a cell nucleus, are consumed by macrophages.

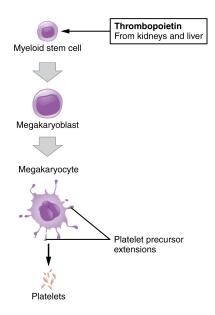
Platelets are relatively small, 2–4 μ m in diameter, but numerous, with typically 150,000–160,000 per μ L of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.

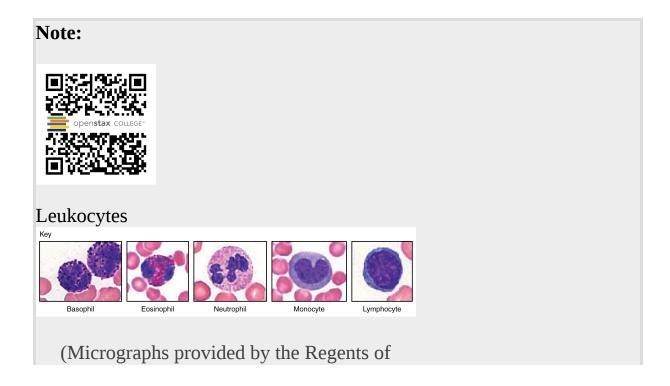
Disorders of Platelets

Thrombocytosis is a condition in which there are too many platelets. This may trigger formation of unwanted blood clots (thrombosis), a potentially fatal disorder. If there is an insufficient number of platelets, called **thrombocytopenia**, blood may not clot properly, and excessive bleeding may result.

Platelets



Platelets are derived from cells called megakaryocytes.



University of Michigan Medical School © 2012)

View University of Michigan Webscopes at http://histology.med.umich.edu/medical/blood-and-bone-marrow and explore the blood slides in greater detail. The Webscope feature allows you to move the slides as you would with a mechanical stage. You can increase and decrease the magnification. There is a chance to review each of the leukocytes individually after you have attempted to identify them from the first two blood smears. In addition, there are a few multiple choice questions.

Are you able to recognize and identify the various formed elements? You will need to do this is a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?

Chapter Review

Leukocytes function in body defenses. They squeeze out of the walls of blood vessels through emigration or diapedesis, then may move through tissue fluid or become attached to various organs where they fight against pathogenic organisms, diseased cells, or other threats to health. Granular leukocytes, which include neutrophils, eosinophils, and basophils, originate with myeloid stem cells, as do the agranular monocytes. The other agranular leukocytes, NK cells, B cells, and T cells, arise from the lymphoid stem cell line. The most abundant leukocytes are the neutrophils, which are first responders to infections, especially with bacteria. About 20–30 percent of all leukocytes are lymphocytes, which are critical to the body's defense against specific threats. Leukemia and lymphoma are malignancies involving leukocytes. Platelets are fragments of cells known

as megakaryocytes that dwell within the bone marrow. While many platelets are stored in the spleen, others enter the circulation and are essential for hemostasis; they also produce several growth factors important for repair and healing.

Glossary

agranular leukocytes

leukocytes with few granules in their cytoplasm; specifically, monocytes, lymphocytes, and NK cells

B lymphocytes

(also, B cells) lymphocytes that defend the body against specific pathogens and thereby provide specific immunity

basophils

granulocytes that stain with a basic (alkaline) stain and store histamine and heparin

defensins

antimicrobial proteins released from neutrophils and macrophages that create openings in the plasma membranes to kill cells

diapedesis

(also, emigration) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

emigration

(also, diapedesis) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

eosinophils

granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

granular leukocytes

leukocytes with abundant granules in their cytoplasm; specifically, neutrophils, eosinophils, and basophils

leukemia

cancer involving leukocytes

leukocyte

(also, white blood cell) colorless, nucleated blood cell, the chief function of which is to protect the body from disease

leukocytosis

excessive leukocyte proliferation

leukopenia

below-normal production of leukocytes

lymphocytes

agranular leukocytes of the lymphoid stem cell line, many of which function in specific immunity

lymphoma

form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues

lysozyme

digestive enzyme with bactericidal properties

megakaryocyte

bone marrow cell that produces platelets

memory cell

type of B or T lymphocyte that forms after exposure to a pathogen

monocytes

agranular leukocytes of the myeloid stem cell line that circulate in the bloodstream; tissue monocytes are macrophages

natural killer (NK) cells

cytotoxic lymphocytes capable of recognizing cells that do not express "self" proteins on their plasma membrane or that contain foreign or abnormal markers; provide generalized, nonspecific immunity

neutrophils

granulocytes that stain with a neutral dye and are the most numerous of the leukocytes; especially active against bacteria

polymorphonuclear

having a lobed nucleus, as seen in some leukocytes

positive chemotaxis

process in which a cell is attracted to move in the direction of chemical stimuli

T lymphocytes

(also, T cells) lymphocytes that provide cellular-level immunity by physically attacking foreign or diseased cells

thrombocytes

platelets, one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

thrombocytopenia

condition in which there are too few platelets, resulting in abnormal bleeding (hemophilia)

thrombocytosis

condition in which there are too many platelets, resulting in abnormal clotting (thrombosis)

OU Human Physiology: Hemostasis By the end of this section, you will be able to:

- List and provide a generalized overview for the three steps in hemostasis
- Compare hemophilia to thrombosis

Platelets are key players in **hemostasis**, the process by which the body seals a ruptured blood vessel and prevents further loss of blood. Although rupture of larger vessels usually requires medical intervention, hemostasis is quite effective in dealing with small, simple wounds. There are three steps to the process: vascular spasm, the formation of a platelet plug, and coagulation (blood clotting). Failure of any of these steps will result in **hemorrhage**—excessive bleeding.

Vascular Spasm

When a vessel is severed or punctured, or when the wall of a vessel is damaged, vascular spasm occurs. In **vascular spasm**, the smooth muscle in the walls of the vessel contracts dramatically. This smooth muscle has both circular layers; larger vessels also have longitudinal layers. The circular layers tend to constrict the flow of blood, whereas the longitudinal layers, when present, draw the vessel back into the surrounding tissue, often making it more difficult for a surgeon to locate, clamp, and tie off a severed vessel. The vascular spasm response is believed to be triggered by several chemicals called endothelins that are released by vessel-lining cells and by pain receptors in response to vessel injury. This phenomenon typically lasts for up to 30 minutes, although it can last for hours.

Formation of the Platelet Plug

In the second step, platelets, which normally float free in the plasma, encounter the area of vessel rupture with the exposed underlying connective tissue and collagenous fibers. The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining. This process is assisted by a glycoprotein in the blood plasma called von Willebrand factor, which helps stabilize the growing **platelet plug**. As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis. Among the substances released by the platelets are:

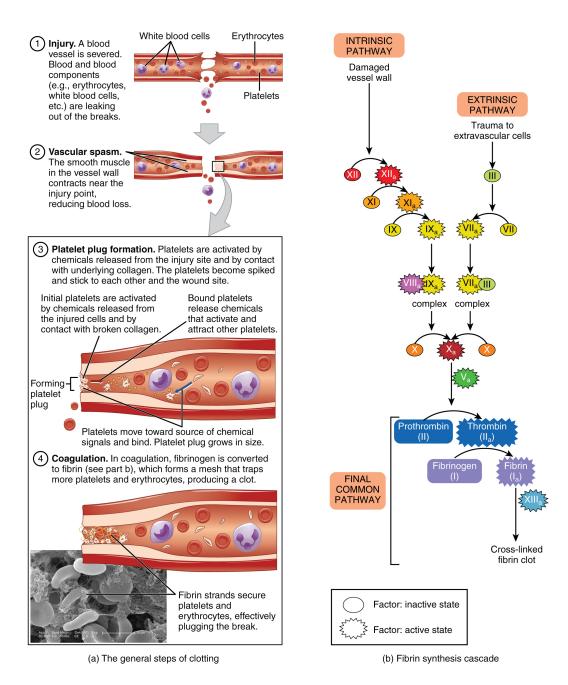
- adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug
- serotonin, which maintains vasoconstriction
- prostaglandins and phospholipids, which also maintain vasoconstriction and help to activate further clotting chemicals, as discussed next

A platelet plug can temporarily seal a small opening in a blood vessel. Plug formation, in essence, buys the body time while more sophisticated and durable repairs are being made. In a similar manner, even modern naval warships still carry an assortment of wooden plugs to temporarily repair small breaches in their hulls until permanent repairs can be made.

Coagulation

Those more sophisticated and more durable repairs are collectively called **coagulation**, the formation of a blood clot. The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall. The result is the production of a gelatinous but robust clot made up of a mesh of **fibrin**—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped. [link] summarizes the three steps of hemostasis.

Hemostasis



(a) An injury to a blood vessel initiates the process of hemostasis. Blood clotting involves three steps. First, vascular spasm constricts the flow of blood. Next, a platelet plug forms to temporarily seal small openings in the vessel. Coagulation then enables the repair of the vessel wall once the leakage of blood has stopped. (b) The synthesis of fibrin in blood clots involves either an intrinsic pathway or an extrinsic pathway, both of which lead to a common pathway. (credit a: Kevin MacKenzie)

Clotting Factors Involved in Coagulation

In the coagulation cascade, chemicals called **clotting factors** (or coagulation factors) prompt reactions that activate still more coagulation factors. The process is complex, but is initiated along two basic pathways:

- The extrinsic pathway, which normally is triggered by trauma.
- The intrinsic pathway, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.

Both of these merge into a third pathway, referred to as the common pathway (see $[\underline{link}]\mathbf{b}$). All three pathways are dependent upon the 12 known clotting factors, including Ca^{2+} and vitamin K ($[\underline{link}]$). Clotting factors are secreted primarily by the liver and the platelets. The liver requires the fat-soluble vitamin K to produce many of them. Vitamin K (along with biotin and folate) is somewhat unusual among vitamins in that it is not only consumed in the diet but is also synthesized by bacteria residing in the large intestine. The calcium ion, considered factor IV, is derived from the diet and from the breakdown of bone. Some recent evidence indicates that activation of various clotting factors occurs on specific receptor sites on the surfaces of platelets.

The 12 clotting factors are numbered I through XIII according to the order of their discovery. Factor VI was once believed to be a distinct clotting factor, but is now thought to be identical to factor V. Rather than renumber the other factors, factor VI was allowed to remain as a placeholder and also a reminder that knowledge changes over time.

Clotting Factors				
Factor number	Name	Type of molecule	Source	Pathway(s)
I	Fibrinogen	Plasma protein	Liver	Common; converted into fibrin

Clotting Factors				
Factor number	Name	Type of molecule	Source	Pathway(s)
II	Prothrombin	Plasma protein	Liver*	Common; converted into thrombin
III	Tissue thromboplastin or tissue factor	Lipoprotein mixture	Damaged cells and platelets	Extrinsic
IV	Calcium ions	Inorganic ions in plasma	Diet, platelets, bone matrix	Entire process
V	Proaccelerin	Plasma protein	Liver, platelets	Extrinsic and intrinsic
VI	Not used	Not used	Not used	Not used
VII	Proconvertin	Plasma protein	Liver *	Extrinsic
VIII	Antihemolytic factor A	Plasma protein factor	Platelets and endothelial cells	Intrinsic; deficiency results in hemophilia A
IX	Antihemolytic factor B (plasma thromboplastin component)	Plasma protein	Liver*	Intrinsic; deficiency results in hemophilia B

Clotting Factors				
Factor number	Name	Type of molecule	Source	Pathway(s)
X	Stuart–Prower factor (thrombokinase)	Protein	Liver*	Extrinsic and intrinsic
XI	Antihemolytic factor C (plasma thromboplastin antecedent)	Plasma protein	Liver	Intrinsic; deficiency results in hemophilia C
XII	Hageman factor	Plasma protein	Liver	Intrinsic; initiates clotting in vitro also activates plasmin
XIII	Fibrin- stabilizing factor	Plasma protein	Liver, platelets	Stabilizes fibrin; slows fibrinolysis

^{*}Vitamin K required.

Extrinsic Pathway

The quicker responding and more direct **extrinsic pathway** (also known as the **tissue factor** pathway) begins when damage occurs to the surrounding tissues, such as in a traumatic injury. Upon contact with blood plasma, the damaged extravascular cells, which are extrinsic to the bloodstream, release factor III (thromboplastin). Sequentially, Ca²⁺ then factor VII (proconvertin), which is activated by factor III, are added, forming an enzyme complex. This enzyme complex leads to activation of factor X (Stuart–Prower factor), which activates the common pathway discussed below. The events in the extrinsic pathway are completed in a matter of seconds.

Intrinsic Pathway

The **intrinsic pathway** (also known as the contact activation pathway) is longer and more complex. In this case, the factors involved are intrinsic to (present within) the bloodstream. The pathway can be prompted by damage to the tissues, resulting from internal factors such as arterial disease; however, it is most often initiated when factor XII (Hageman factor) comes into contact with foreign materials, such as when a blood sample is put into a glass test tube. Within the body, factor XII is typically activated when it encounters negatively charged molecules, such as inorganic polymers and phosphate produced earlier in the series of intrinsic pathway reactions. Factor XII sets off a series of reactions that in turn activates factor XI (antihemolytic factor C or plasma thromboplastin antecedent) then factor IX (antihemolytic factor B or plasma thromboplasmin). In the meantime, chemicals released by the platelets increase the rate of these activation reactions. Finally, factor VIII (antihemolytic factor A) from the platelets and endothelial cells combines with factor IX (antihemolytic factor B or plasma thromboplasmin) to form an enzyme complex that activates factor X (Stuart– Prower factor or thrombokinase), leading to the common pathway. The events in the intrinsic pathway are completed in a few minutes.

Common Pathway

Both the intrinsic and extrinsic pathways lead to the **common pathway**, in which fibrin is produced to seal off the vessel. Once factor X has been activated by either the intrinsic or extrinsic pathway, the enzyme prothrombinase converts factor II, the inactive enzyme prothrombin, into the active enzyme **thrombin**. (Note that if the enzyme thrombin were not normally in an inactive form, clots would form spontaneously, a condition not consistent with life.) Then, thrombin converts factor I, the insoluble fibrinogen, into the soluble fibrin protein strands. Factor XIII then stabilizes the fibrin clot.

Fibrinolysis

The stabilized clot is acted upon by contractile proteins within the platelets. As these proteins contract, they pull on the fibrin threads, bringing the edges of the clot more tightly together, somewhat as we do when tightening loose shoelaces (see [link]a). This process also wrings out of the clot a small amount of fluid called **serum**, which is blood plasma without its clotting factors.

To restore normal blood flow as the vessel heals, the clot must eventually be removed. **Fibrinolysis** is the gradual degradation of the clot. Again, there is a fairly complicated

series of reactions that involves factor XII and protein-catabolizing enzymes. During this process, the inactive protein plasminogen is converted into the active **plasmin**, which gradually breaks down the fibrin of the clot. Additionally, bradykinin, a vasodilator, is released, reversing the effects of the serotonin and prostaglandins from the platelets. This allows the smooth muscle in the walls of the vessels to relax and helps to restore the circulation.

Plasma Anticoagulants

An **anticoagulant** is any substance that opposes coagulation. Several circulating plasma anticoagulants play a role in limiting the coagulation process to the region of injury and restoring a normal, clot-free condition of blood. For instance, a cluster of proteins collectively referred to as the protein C system inactivates clotting factors involved in the intrinsic pathway. TFPI (tissue factor pathway inhibitor) inhibits the conversion of the inactive factor VII to the active form in the extrinsic pathway. **Antithrombin** inactivates factor X and opposes the conversion of prothrombin (factor II) to thrombin in the common pathway. And as noted earlier, basophils release **heparin**, a short-acting anticoagulant that also opposes prothrombin. Heparin is also found on the surfaces of cells lining the blood vessels. A pharmaceutical form of heparin is often administered therapeutically, for example, in surgical patients at risk for blood clots.

Note:



View these <u>animations</u> to explore the intrinsic, extrinsic, and common pathways that are involved the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

Disorders of Clotting

Either an insufficient or an excessive production of platelets can lead to severe disease or death. As discussed earlier, an insufficient number of platelets, called thrombocytopenia, typically results in the inability of blood to form clots. This can lead to excessive bleeding, even from minor wounds.

Another reason for failure of the blood to clot is the inadequate production of functional amounts of one or more clotting factors. This is the case in the genetic disorder **hemophilia**, which is actually a group of related disorders, the most common of which is hemophilia A, accounting for approximately 80 percent of cases. This disorder results in the inability to synthesize sufficient quantities of factor VIII. Hemophilia B is the second most common form, accounting for approximately 20 percent of cases. In this case, there is a deficiency of factor IX. Both of these defects are linked to the X chromosome and are typically passed from a healthy (carrier) mother to her male offspring, since males are XY. Females would need to inherit a defective gene from each parent to manifest the disease, since they are XX. Patients with hemophilia bleed from even minor internal and external wounds, and leak blood into joint spaces after exercise and into urine and stool. Hemophilia C is a rare condition that is triggered by an autosomal (not sex) chromosome that renders factor XI nonfunctional. It is not a true recessive condition, since even individuals with a single copy of the mutant gene show a tendency to bleed. Regular infusions of clotting factors isolated from healthy donors can help prevent bleeding in hemophiliac patients. At some point, genetic therapy will become a viable option.

In contrast to the disorders characterized by coagulation failure is thrombocytosis, also mentioned earlier, a condition characterized by excessive numbers of platelets that increases the risk for excessive clot formation, a condition known as **thrombosis**. A **thrombus** (plural = thrombi) is an aggregation of platelets, erythrocytes, and even WBCs typically trapped within a mass of fibrin strands. While the formation of a clot is normal following the hemostatic mechanism just described, thrombi can form within an intact or only slightly damaged blood vessel. In a large vessel, a thrombus will adhere to the vessel wall and decrease the flow of blood, and is referred to as a mural thrombus. In a small vessel, it may actually totally block the flow of blood and is termed an occlusive thrombus. Thrombi are most commonly caused by vessel damage to the endothelial lining, which activates the clotting mechanism. These may include venous stasis, when blood in the veins, particularly in the legs, remains stationary for long periods. This is one of the dangers of long airplane flights in crowded conditions and may lead to deep vein thrombosis or atherosclerosis, an accumulation of debris in arteries. Thrombophilia, also called hypercoagulation, is a condition in which there is a tendency to form thrombosis. This may be familial (genetic) or acquired. Acquired forms include the autoimmune disease lupus, immune reactions to heparin, polycythemia vera, thrombocytosis, sickle cell disease, pregnancy, and even obesity. A thrombus can seriously impede blood flow to or from

a region and will cause a local increase in blood pressure. If flow is to be maintained, the heart will need to generate a greater pressure to overcome the resistance.

When a portion of a thrombus breaks free from the vessel wall and enters the circulation, it is referred to as an **embolus**. An embolus that is carried through the bloodstream can be large enough to block a vessel critical to a major organ. When it becomes trapped, an embolus is called an embolism. In the heart, brain, or lungs, an embolism may accordingly cause a heart attack, a stroke, or a pulmonary embolism. These are medical emergencies.

Among the many known biochemical activities of aspirin is its role as an anticoagulant. Aspirin (acetylsalicylic acid) is very effective at inhibiting the aggregation of platelets. It is routinely administered during a heart attack or stroke to reduce the adverse effects. Physicians sometimes recommend that patients at risk for cardiovascular disease take a low dose of aspirin on a daily basis as a preventive measure. However, aspirin can also lead to serious side effects, including increasing the risk of ulcers. A patient is well advised to consult a physician before beginning any aspirin regimen.

A class of drugs collectively known as thrombolytic agents can help speed up the degradation of an abnormal clot. If a thrombolytic agent is administered to a patient within 3 hours following a thrombotic stroke, the patient's prognosis improves significantly. However, some strokes are not caused by thrombi, but by hemorrhage. Thus, the cause must be determined before treatment begins. Tissue plasminogen activator is an enzyme that catalyzes the conversion of plasminogen to plasmin, the primary enzyme that breaks down clots. It is released naturally by endothelial cells but is also used in clinical medicine. New research is progressing using compounds isolated from the venom of some species of snakes, particularly vipers and cobras, which may eventually have therapeutic value as thrombolytic agents.

Chapter Review

Hemostasis is the physiological process by which bleeding ceases. Hemostasis involves three basic steps: vascular spasm, the formation of a platelet plug, and coagulation, in which clotting factors promote the formation of a fibrin clot. Fibrinolysis is the process in which a clot is degraded in a healing vessel. Anticoagulants are substances that oppose coagulation. They are important in limiting the extent and duration of clotting. Inadequate clotting can result from too few platelets, or inadequate production of clotting factors, for instance, in the genetic disorder hemophilia. Excessive clotting, called thrombosis, can be caused by excessive numbers of platelets. A thrombus is a collection of fibrin, platelets, and erythrocytes that has accumulated along the lining of a blood vessel, whereas an

embolus is a thrombus that has broken free from the vessel wall and is circulating in the bloodstream.

Glossary

anticoagulant

substance such as heparin that opposes coagulation

antithrombin

anticoagulant that inactivates factor X and opposes the conversion of prothrombin (factor II) into thrombin in the common pathway

clotting factors

group of 12 identified substances active in coagulation

coagulation

formation of a blood clot; part of the process of hemostasis

common pathway

final coagulation pathway activated either by the intrinsic or the extrinsic pathway, and ending in the formation of a blood clot

embolus

thrombus that has broken free from the blood vessel wall and entered the circulation

extrinsic pathway

initial coagulation pathway that begins with tissue damage and results in the activation of the common pathway

fibrin

insoluble, filamentous protein that forms the structure of a blood clot

fibrinolysis

gradual degradation of a blood clot

hemophilia

genetic disorder characterized by inadequate synthesis of clotting factors

hemorrhage

excessive bleeding

hemostasis

physiological process by which bleeding ceases

heparin

short-acting anticoagulant stored in mast cells and released when tissues are injured, opposes prothrombin

intrinsic pathway

initial coagulation pathway that begins with vascular damage or contact with foreign substances, and results in the activation of the common pathway

plasmin

blood protein active in fibrinolysis

platelet plug

accumulation and adhesion of platelets at the site of blood vessel injury

serum

blood plasma that does not contain clotting factors

thrombin

enzyme essential for the final steps in formation of a fibrin clot

thrombosis

excessive clot formation

thrombus

aggregation of fibrin, platelets, and erythrocytes in an intact artery or vein

tissue factor

protein thromboplastin, which initiates the extrinsic pathway when released in response to tissue damage

vascular spasm

initial step in hemostasis, in which the smooth muscle in the walls of the ruptured or damaged blood vessel contracts

OU Human Physiology: Blood Typing By the end of this section, you will be able to:

- Compare and contrast the ABO and Rh groups including antigens and antibodies
- Identify which blood groups may be safely transfused into patients with different ABO types
- Describe the two basic physiological consequences of transfusion of incompatible blood types
- Explain why erythroblastosis fetalis occurs in infants
- Determine blood types via cross matching
- Discuss why O is a universal donor
- Discuss why AB⁺ is a universal recipient

Blood transfusions in humans were risky procedures until the discovery of the major human blood groups by Karl Landsteiner, an Austrian biologist and physician, in 1900. Until that point, physicians did not understand that death sometimes followed blood transfusions, when the type of donor blood infused into the patient was incompatible with the patient's own blood. Blood groups are determined by the presence or absence of specific marker molecules on the plasma membranes of erythrocytes. With their discovery, it became possible for the first time to match patient-donor blood types and prevent transfusion reactions and deaths.

Antigens, Antibodies, and Transfusion Reactions

Antigens are substances that the body does not recognize as belonging to the "self" and that therefore trigger a defensive response from the leukocytes of the immune system. (Seek more content for additional information on immunity.) Here, we will focus on the role of immunity in blood transfusion reactions. With RBCs in particular, you may see the antigens referred to as isoantigens or agglutinogens (surface antigens) and the antibodies referred to as isoantibodies or agglutinins. In this chapter, we will use the more common terms antigens and antibodies.

Antigens are generally large proteins, but may include other classes of organic molecules, including carbohydrates, lipids, and nucleic acids. Following an infusion of incompatible blood, erythrocytes with foreign antigens appear in the bloodstream and trigger an immune response. Proteins called antibodies (immunoglobulins), which are produced by certain B lymphocytes called plasma cells, attach to the antigens on the plasma membranes of the infused erythrocytes and cause them to adhere to one another.

- Because the arms of the Y-shaped antibodies attach randomly to more than one nonself erythrocyte surface, they form clumps of erythrocytes. This process is called **agglutination**.
- The clumps of erythrocytes block small blood vessels throughout the body, depriving tissues of oxygen and nutrients.
- As the erythrocyte clumps are degraded, in a process called **hemolysis**, their hemoglobin is released into the bloodstream. This hemoglobin travels to the kidneys, which are responsible for filtration of the blood. However, the load of hemoglobin released can easily overwhelm the kidney's capacity to clear it, and the patient can quickly develop kidney failure.

More than 50 antigens have been identified on erythrocyte membranes, but the most significant in terms of their potential harm to patients are classified in two groups: the ABO blood group and the Rh blood group.

The ABO Blood Group

Although the **ABO blood group** name consists of three letters, ABO blood typing designates the presence or absence of just two antigens, A and B. Both are glycoproteins. People whose erythrocytes have A antigens on their erythrocyte membrane surfaces are designated blood type A, and those whose erythrocytes have B antigens are blood type B. People can also have both A and B antigens on their erythrocytes, in which case they are blood type AB. People with neither A nor B antigens are designated blood type O. ABO blood types are genetically determined.

Normally the body must be exposed to a foreign antigen before an antibody can be produced. This is not the case for the ABO blood group. Individuals with type A blood—without any prior exposure to incompatible blood—have preformed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has pre-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have preformed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

Rh Blood Groups

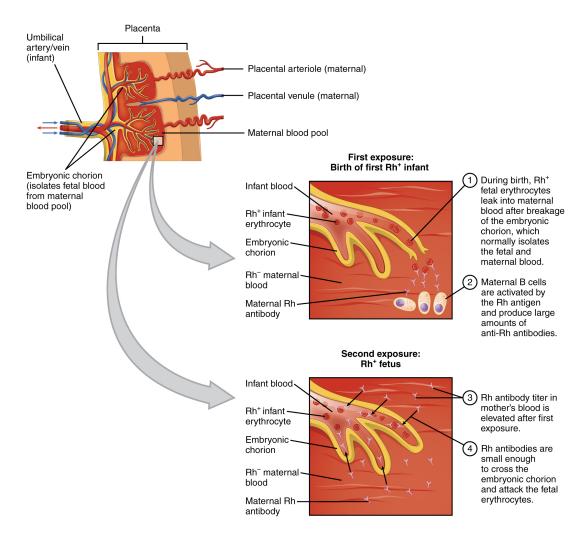
The **Rh blood group** is classified according to the presence or absence of a second erythrocyte antigen identified as Rh. (It was first discovered in a type of primate known as a rhesus macaque, which is often used in research, because its blood is similar to that of humans.) Although dozens of Rh antigens have been identified, only one, designated D, is clinically important. Those who have the Rh D antigen present on their erythrocytes—about 85 percent of Americans—are described as Rh positive (Rh⁺) and those who lack it are Rh negative (Rh⁻). Note that the Rh group is distinct from the ABO group, so any individual, no matter their ABO blood type, may have or lack this Rh antigen. When identifying a patient's blood type, the Rh group is designated by adding the word positive or negative to the ABO type. For example, A positive (A⁺) means ABO group A blood with the Rh antigen present, and AB negative (AB⁻) means ABO group AB blood without the Rh antigen.

[link] summarizes the distribution of the ABO and Rh blood types within the United States.

Summary of ABO and Rh Blood Types within the United States				
Blood Type	African- Americans	Asian- Americans	Caucasian- Americans	Latino/Latina- Americans
A^+	24	27	33	29
A ⁻	2	0.5	7	2
B^{+}	18	25	9	9
B^-	1	0.4	2	1
AB^+	4	7	3	2
AB^-	0.3	0.1	1	0.2
O ⁺	47	39	37	53

Summary of ABO and Rh Blood Types within the United States				
Blood Type	African- Americans	Asian- Americans	Caucasian- Americans	Latino/Latina- Americans
O ⁻	4	1	8	4

In contrast to the ABO group antibodies, which are preformed, antibodies to the Rh antigen are produced only in Rh⁻ individuals after exposure to the antigen. This process, called sensitization, occurs following a transfusion with Rh-incompatible blood or, more commonly, with the birth of an Rh⁺ baby to an Rh⁻ mother. Problems are rare in a first pregnancy, since the baby's Rh⁺ cells rarely cross the placenta (the organ of gas and nutrient exchange between the baby and the mother). However, during or immediately after birth, the Rh⁻ mother can be exposed to the baby's Rh⁺ cells ([link]). Research has shown that this occurs in about 13–14 percent of such pregnancies. After exposure, the mother's immune system begins to generate anti-Rh antibodies. If the mother should then conceive another Rh⁺ baby, the Rh antibodies she has produced can cross the placenta into the fetal bloodstream and destroy the fetal RBCs. This condition, known as **hemolytic disease of the newborn (HDN)** or erythroblastosis fetalis, may cause anemia in mild cases, but the agglutination and hemolysis can be so severe that without treatment the fetus may die in the womb or shortly after birth. Erythroblastosis Fetalis



The first exposure of an Rh⁻ mother to Rh⁺ erythrocytes during pregnancy induces sensitization. Anti-Rh antibodies begin to circulate in the mother's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh⁺ fetus in the uterus. Maternal anti-Rh antibodies may cross the placenta and enter the fetal bloodstream, causing agglutination and hemolysis of fetal erythrocytes.

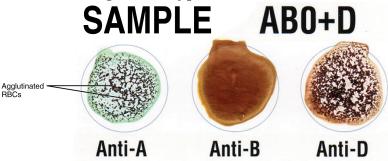
A drug known as RhoGAM, short for Rh immune globulin, can temporarily prevent the development of Rh antibodies in the Rh⁻ mother, thereby averting this potentially serious disease for the fetus. RhoGAM antibodies destroy any fetal Rh⁺ erythrocytes that may cross the placental barrier. RhoGAM is normally administered to Rh⁻ mothers during weeks 26–28 of pregnancy and within 72 hours following birth. It has proven remarkably effective in decreasing the

incidence of HDN. Earlier we noted that the incidence of HDN in an Rh⁺ subsequent pregnancy to an Rh⁻ mother is about 13–14 percent without preventive treatment. Since the introduction of RhoGAM in 1968, the incidence has dropped to about 0.1 percent in the United States.

ABO Cross Matching

Clinicians are able to determine a patient's blood type quickly and easily using commercially prepared antibodies. In this laboratory test, called **cross matching**, a sample of blood of unknown type is placed into separate wells. Into one well a small amount of anti-A antibody is added, and to another a small amount of anti-B antibody. If the antigen is present, the antibodies will cause visible agglutination of the cells ([link]). The blood should also be tested for Rh antibodies.

Cross Matching Blood Types



This sample of a commercially produced "bedside" card enables quick typing of both a recipient's and donor's blood before transfusion. The card contains three reaction sites or wells. One is coated with an anti-A antibody, one with an anti-B antibody, and one with an anti-D antibody (tests for the presence of Rh factor D). Mixing a drop of blood and saline into each well enables the blood to interact with a preparation of type-specific antibodies, also called antiseras. Agglutination of RBCs in a given site indicates a positive identification of the blood antigens, in this case A and Rh antigens for blood type A⁺. For the purpose of transfusion, the donor's and recipient's blood types must match.

ABO Transfusion Protocols

To avoid transfusion reactions, it is best to transfuse only matching blood types: that is, a type B⁺ recipient should ideally receive blood only from a type B⁺ donor and so on. That said, in emergency situations, when acute hemorrhage threatens the patient's life, there may not be time for cross matching to identify blood type. In these cases, blood from a **universal donor**—an individual with type O⁻ blood may be transfused. Recall that type O erythrocytes do not display A or B antigens. Thus, anti-A or anti-B antibodies that might be circulating in the patient's blood plasma will not encounter any erythrocyte surface antigens on the donated blood and therefore will not be provoked into a response. One problem with this designation of universal donor is if the O⁻ individual had prior exposure to Rh antigen, Rh antibodies may be present in the donated blood. Also, introducing type O blood into an individual with type A, B, or AB blood will nevertheless introduce antibodies against both A and B antigens, as these are always circulating in the type O blood plasma. This may cause problems for the recipient, but because the volume of blood transfused is much lower than the volume of the patient's own blood, the adverse effects of the relatively few infused plasma antibodies are typically limited. Rh factor also plays a role. If Rh⁻ individuals receiving blood have had prior exposure to Rh antigen, antibodies for this antigen may be present in the blood and trigger agglutination to some degree. Although it is always preferable to cross match a patient's blood before transfusing, in a true life-threatening emergency situation, this is not always possible, and these procedures may be implemented.

A patient with blood type AB⁺ is known as the **universal recipient**. This patient can theoretically receive any type of blood, because the patient's own blood—having both A and B antigens on the erythrocyte surface—does not produce anti-A or anti-B antibodies. In addition, an Rh⁺ patient can receive both Rh⁺ and Rh⁻ blood. However, keep in mind that the donor's blood will contain circulating antibodies, again with possible negative implications. [link] summarizes the blood types and compatibilities.

At the scene of multiple-vehicle accidents, military engagements, and natural or human-caused disasters, many victims may suffer simultaneously from acute hemorrhage, yet type O blood may not be immediately available. In these circumstances, medics may at least try to replace some of the volume of blood that has been lost. This is done by intravenous administration of a saline solution that provides fluids and electrolytes in proportions equivalent to those of normal blood plasma. Research is ongoing to develop a safe and effective artificial blood that

would carry out the oxygen-carrying function of blood without the RBCs, enabling transfusions in the field without concern for incompatibility. These blood substitutes normally contain hemoglobin- as well as perfluorocarbon-based oxygen carriers.

ABO Blood Group

	віоод туре				
	А	В	AB	0	
Red Blood Cell Type		B	AB		
Antibodies in Plasma	Anti-B	Anti-A	None	Anti-A and Anti-B	
Antigens in Red blood Cell	A antigen	♦ B antigen	A and B antigens	None	
Blood Types Compatible in an Emergency	A, O	B, O	A, B, AB, O (AB ⁺ is the universal recipient)	O (O is the universal donor)	

Blood Type

This chart summarizes the characteristics of the blood types in the ABO blood group. See the text for more on the concept of a universal donor or recipient.

Chapter Review

Antigens are nonself molecules, usually large proteins, which provoke an immune response. In transfusion reactions, antibodies attach to antigens on the surfaces of erythrocytes and cause agglutination and hemolysis. ABO blood group antigens are designated A and B. People with type A blood have A antigens on their erythrocytes, whereas those with type B blood have B antigens. Those with AB blood have both A and B antigens, and those with type O blood have neither A nor B antigens. The blood plasma contains preformed antibodies against the antigens not present on a person's erythrocytes.

A second group of blood antigens is the Rh group, the most important of which is Rh D. People with Rh⁻ blood do not have this antigen on their erythrocytes,

whereas those who are Rh⁺ do. About 85 percent of Americans are Rh⁺. When a woman who is Rh⁻ becomes pregnant with an Rh⁺ fetus, her body may begin to produce anti-Rh antibodies. If she subsequently becomes pregnant with a second Rh⁺ fetus and is not treated preventively with RhoGAM, the fetus will be at risk for an antigen-antibody reaction, including agglutination and hemolysis. This is known as hemolytic disease of the newborn.

Cross matching to determine blood type is necessary before transfusing blood, unless the patient is experiencing hemorrhage that is an immediate threat to life, in which case type O⁻ blood may be transfused.

Glossary

ABO blood group

blood-type classification based on the presence or absence of A and B glycoproteins on the erythrocyte membrane surface

agglutination

clustering of cells into masses linked by antibodies

cross matching

blood test for identification of blood type using antibodies and small samples of blood

hemolysis

destruction (lysis) of erythrocytes and the release of their hemoglobin into circulation

hemolytic disease of the newborn (HDN)

(also, erythroblastosis fetalis) disorder causing agglutination and hemolysis in an Rh⁺ fetus or newborn of an Rh⁻ mother

Rh blood group

blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface

universal donor

individual with type O⁻ blood

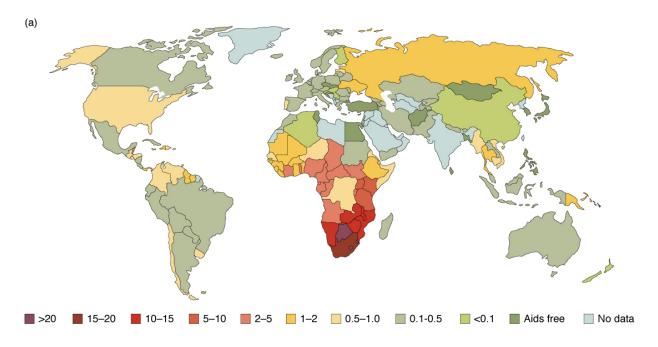
universal recipient

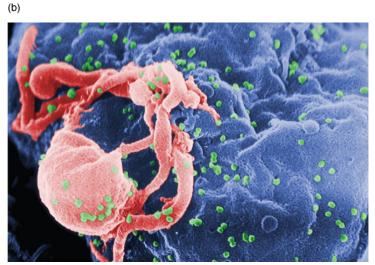
individual with type AB+ blood

OU Human Physiology: Lymphatic and Immune System Introduction class="introduction"

The Worldwide AIDS Epidemic

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(a) As of
2008, more
  than 15
percent of
adults were
  infected
with HIV in
  certain
  African
 countries.
 This grim
picture had
 changed
  little by
2012. (b) In
    this
 scanning
  electron
micrograph
   , HIV
  virions
  (green
 particles)
are budding
  off the
surface of a
macrophag
  e (pink
structure).
(credit b: C.
Goldsmith)
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Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Identify the components and anatomy of the lymphatic system
- Discuss the functions of the lymphatic system
- Discuss the role of the innate immune response against pathogens
- Describe the power of the adaptive immune response to cure disease

- Explain immunological deficiencies and over-reactions of the immune system
- Discuss the role of the immune response in transplantation and cancer
- Describe the interaction of the immune and lymphatic systems with other body systems

In June 1981, the Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia, published a report of an unusual cluster of five patients in Los Angeles, California. All five were diagnosed with a rare pneumonia caused by a fungus called *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*).

Why was this unusual? Although commonly found in the lungs of healthy individuals, this fungus is an opportunistic pathogen that causes disease in individuals with suppressed or underdeveloped immune systems. The very young, whose immune systems have yet to mature, and the elderly, whose immune systems have declined with age, are particularly susceptible. The five patients from LA, though, were between 29 and 36 years of age and should have been in the prime of their lives, immunologically speaking. What could be going on?

A few days later, a cluster of eight cases was reported in New York City, also involving young patients, this time exhibiting a rare form of skin cancer known as Kaposi's sarcoma. This cancer of the cells that line the blood and lymphatic vessels was previously observed as a relatively innocuous disease of the elderly. The disease that doctors saw in 1981 was frighteningly more severe, with multiple, fast-growing lesions that spread to all parts of the body, including the trunk and face. Could the immune systems of these young patients have been compromised in some way? Indeed, when they were tested, they exhibited extremely low numbers of a specific type of white blood cell in their bloodstreams, indicating that they had somehow lost a major part of the immune system.

Acquired immune deficiency syndrome, or AIDS, turned out to be a new disease caused by the previously unknown human immunodeficiency virus

(HIV). Although nearly 100 percent fatal in those with active HIV infections in the early years, the development of anti-HIV drugs has transformed HIV infection into a chronic, manageable disease and not the certain death sentence it once was. One positive outcome resulting from the emergence of HIV disease was that the public's attention became focused as never before on the importance of having a functional and healthy immune system. The immune system however, is not limited to viral infections.

OU Human Physiology: Anatomy of the Lymphatic and Immune Systems By the end of this section, you will be able to:

- Describe the structure function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Briefly compare and contrast the innate and adaptive immune responses
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system
- Compare and contrast primary and secondary lymphatic organs in terms of development, maturation, and activation
- Describe the location and function of each primary and secondary lymphatic organ

The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial

fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes "backs up" from the lymph vessels) in the tissue spaces. This inappropriate accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

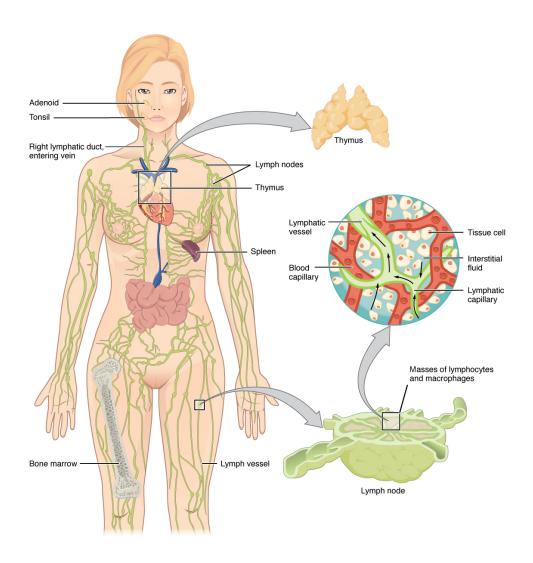
As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.

Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body ([link]).

Anatomy of the Lymphatic System



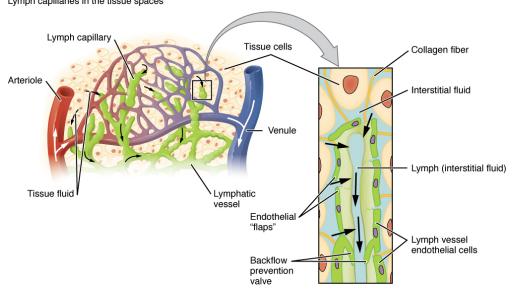
Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.

A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.

Lymphatic Capillaries

Lymphatic capillaries, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body ([link]). Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

Lymphatic Capillaries Lymph capillaries in the tissue spaces



Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells (see [link]). When interstitial pressure is low, the endothelial flaps close to prevent "backflow." As interstitial pressure increases, the spaces between the cells open up, allowing the fluid

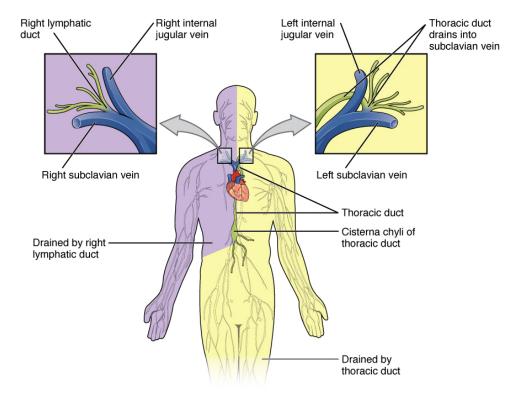
to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called **chyle**. The chyle then travels through the lymphatic system, eventually entering the liver and then the bloodstream.

Larger Lymphatic Vessels, Trunks, and Ducts

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance (see [link]).

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct ([link]). On the left side of the body, the remaining portions of the body drain into the larger thoracic duct, which drains into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the cisterna chyli, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk. Major Trunks and Ducts of the Lymphatic System



The thoracic duct drains a much larger portion of the body than does the right lymphatic duct.

The overall drainage system of the body is asymmetrical (see [link]). The right lymphatic duct receives lymph from only the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the **thoracic duct** via all the remaining lymphatic trunks. In general, lymphatic vessels of the subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

The Organization of Immune Function

The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases

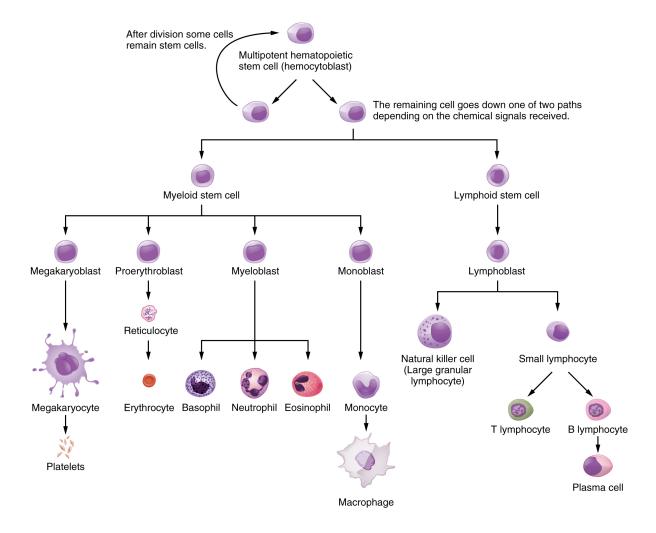
based on the timing of their effects. The three temporal phases consist of the following:

- **Barrier defenses** such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
- The rapid but nonspecific **innate immune response**, which consists of a variety of specialized cells and soluble factors
- The slower but more specific and effective **adaptive (or aquired) immune response**, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses

The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells ([link]). In contrast with embryonic stem cells, hematopoietic stem cells are present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function. These cells can be divided into three classes based on function:

- Phagocytic cells, which ingest pathogens to destroy them
- Lymphocytes, which specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help mediate immune responses against parasites and intracellular pathogens such as viruses

Hematopoietic System of the Bone Marrow



All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.

Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses ([link]). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B

cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An **antibody** is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An **antigen** is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.

T Cells

The **T cell**, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

Another type of lymphocyte of importance is the plasma cell. A **plasma cell** is a B cell that has differentiated in response to antigen binding, and has thereby gained the ability to secrete soluble antibodies. These cells differ in morphology from standard B and T cells in that they contain a large amount

of cytoplasm packed with the protein-synthesizing machinery known as rough endoplasmic reticulum.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A **natural killer cell (NK)** is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body's first lines of defense against viruses and certain types of cancer.

Lymphocytes			
Type of lymphocyte	Primary function		
B lymphocyte	Generates diverse antibodies		
T lymphocyte	Secretes chemical messengers		
Plasma cell	Secretes antibodies		
NK cell	Destroys virally infected cells		

Primary Lymphoid Organs and Lymphocyte Development

Understanding the differentiation and development of B and T cells is critical to the understanding of the adaptive immune response. It is through this process that the body (ideally) learns to destroy only pathogens and leaves the body's own cells relatively intact. The **primary lymphoid**

organs (also called central lymphoid organs) are the bone marrow, and thymus gland. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.

Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red **bone marrow** is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells ([link]). The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a **thymocyte**, leaves the bone marrow and matures largely in the thymus gland.

Bone Marrow



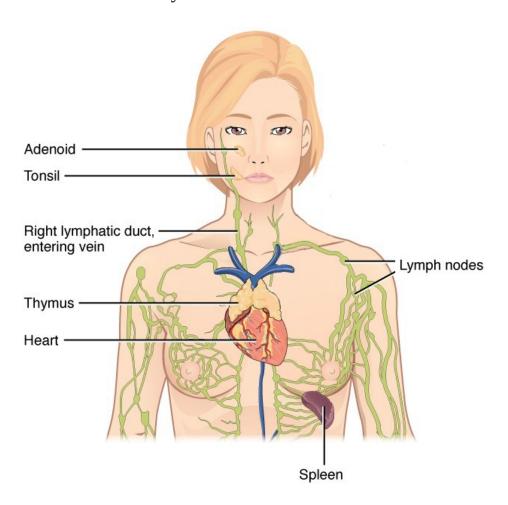
Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible

in the center. The white reference bar is 1 cm.

Thymus

The **thymus** gland is a bilobed organ found in the space between the sternum and the aorta of the heart ([link]). Connective tissue holds the lobes closely together but also separates them and forms a capsule.

Location of the Thymus



The thymus lies above the heart.

The thymus contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes).

Secondary Lymphoid Organs and their Roles in Active Immune Responses

Lymphocytes develop and mature in the primary lymphoid organs, but they mount immune responses from the **secondary lymphoid organs** (also called peripheral lymphoid organs). A **naïve lymphocyte** is one that has left the primary organ and entered a secondary lymphoid organ. Naïve lymphocytes are fully functional immunologically, but have yet to encounter an antigen to respond to. In addition to circulating in the blood and lymph, lymphocytes concentrate in secondary lymphoid organs, which include the lymph nodes, spleen, and lymphoid nodules. All of these tissues have many features in common, including the following:

- The presence of lymphoid follicles, the sites of the formation of lymphocytes, with specific B cell-rich and T cell-rich areas
- An internal structure of reticular fibers with associated fixed macrophages
- Germinal centers, which are the sites of rapidly dividing B lymphocytes and plasma cells, with the exception of the spleen
- Specialized post-capillary vessels known as high endothelial venules; the cells lining these venules are thicker and more columnar than normal endothelial cells, which allow cells from the blood to directly enter these tissues

Lymph Nodes

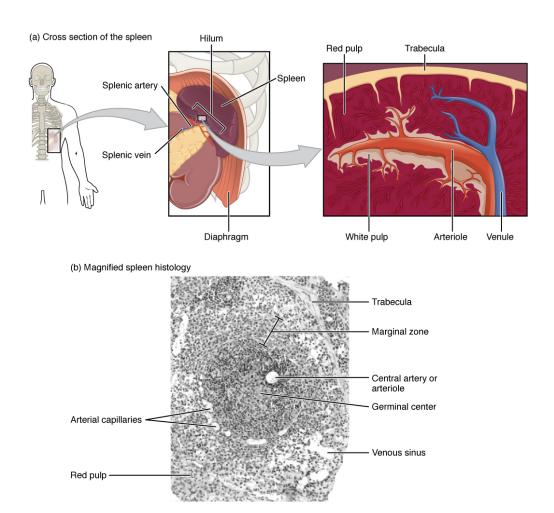
Lymph nodes function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the "filters of the lymph" ([link]). Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many of the pathogens

that pass through, thereby removing them from the body. The lymph node is also the site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system.

Spleen

In addition to the lymph nodes, the **spleen** is a major secondary lymphoid organ ([link]). It is about 12 cm (5 in) long and is attached to the lateral border of the stomach. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the "filter of the blood" because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

Spleen



(a) The spleen is attached to the stomach. (b) A micrograph of spleen tissue shows the germinal center. The marginal zone is the region between the red pulp and white pulp, which sequesters particulate antigens from the circulation and presents these antigens to lymphocytes in the white pulp. EM × 660. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

The spleen is also divided by trabeculae of connective tissue, and within each splenic nodule is an area of red pulp, consisting of mostly red blood cells, and white pulp, which resembles the lymphoid follicles of the lymph nodes. Upon entering the spleen, the splenic artery splits into several

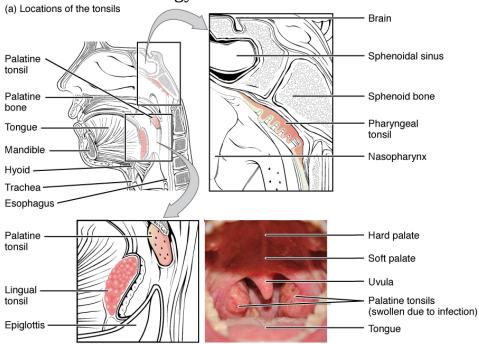
arterioles (surrounded by white pulp) and eventually into sinusoids. Blood from the capillaries subsequently collects in the venous sinuses and leaves via the splenic vein. The red pulp consists of reticular fibers with fixed macrophages attached, free macrophages, and all of the other cells typical of the blood, including some lymphocytes. The white pulp surrounds a central arteriole and consists of germinal centers of dividing B cells surrounded by T cells and accessory cells, including macrophages and dendritic cells. Thus, the red pulp primarily functions as a filtration system of the blood, using cells of the relatively nonspecific immune response, and white pulp is where adaptive T and B cell responses are mounted.

Lymphoid Nodules

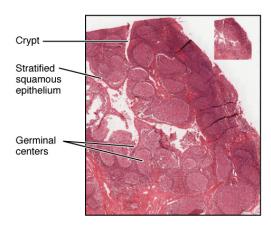
The other lymphoid tissues, the **lymphoid nodules**, have a simpler architecture than the spleen and lymph nodes in that they consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens.

Tonsils are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens ([link]). The tonsil located at the back of the throat, the pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually "encourage" pathogens to penetrate deep into the tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils—to help children's bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

Locations and Histology of the Tonsils



(b) Histology of palatine tonsil



(a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances ([link]). Peyer's patches contain specialized endothelial cells called M (or microfold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.

Mucosa-associated Lymphoid Tissue (MALT) Nodule



LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Bronchus-associated lymphoid tissue (BALT) consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

Glossary

adaptive immune response

(also called, acquired immune response) relatively slow but very specific and effective immune response controlled by lymphocytes

antibody

antigen-specific protein secreted by plasma cells; immunoglobulin

antigen

molecule recognized by the receptors of B and T lymphocytes

barrier defenses

antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection

B cells

lymphocytes that act by differentiating into an antibody-secreting plasma cell

bone marrow

tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

bronchus-associated lymphoid tissue (BALT)

lymphoid nodule associated with the respiratory tract

chyle

lipid-rich lymph inside the lymphatic capillaries of the small intestine

immune system

series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

innate immune response

rapid but relatively nonspecific immune response

lymph

fluid contained within the lymphatic system

lymph node

one of the bean-shaped organs found associated with the lymphatic vessels

lymphatic capillaries

smallest of the lymphatic vessels and the origin of lymph flow

lymphatic system

network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream.

lymphatic trunks

large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

lymphocytes

white blood cells characterized by a large nucleus and small rim of cytoplasm

lymphoid nodules

unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT)

lymphoid nodule associated with the mucosa

naïve lymphocyte

mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK)

cytotoxic lymphocyte of innate immune response

plasma cell

differentiated B cell that is actively secreting antibody

primary lymphoid organ

(also called, central lymphoid organs) site where lymphocytes mature and proliferate; red bone marrow and thymus gland

secondary lymphoid organs

(also called, peripheral lymphoid organs) sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

spleen

secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell

lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

thoracic duct

large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte

immature T cell found in the thymus

thymus

primary lymphoid organ; where T lymphocytes proliferate and mature

tonsils

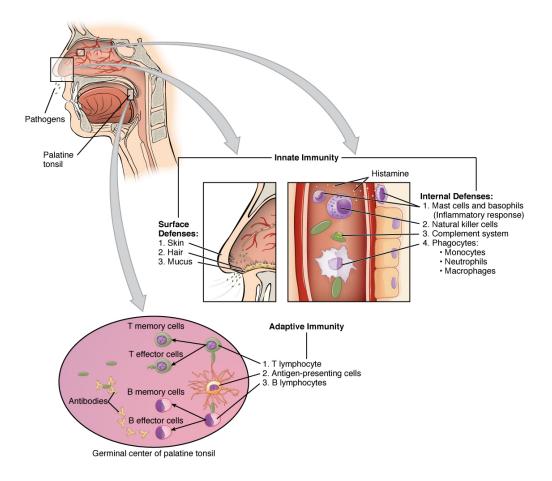
lymphoid nodules associated with the nasopharynx

OU Human Physiology: Barrier Defenses and the Innate Immune Response By the end of this section, you will be able to:

- Show how the innate immune response is important and how it helps guide and prepare the body for adaptive immune responses
- Describe each of the barrier defenses of the body
- List and discuss the function of each cell type involved in the innate immune response
- Describe the process of chemotaxis used by phagocytic immune cells
- Describe the function of interferon
- Summarize the alternate pathway of the complement system
- Create a concept map to explain the steps of inflammation and how they lead to destruction of a pathogen
- Relate the process of inflammation to the four characteristics of inflammation

The immune system can be divided into two overlapping mechanisms to destroy pathogens: the innate immune response, which is relatively rapid but nonspecific and thus not always effective, and the adaptive immune response, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens ([link]).

Cooperation between Innate and Adaptive Immune Responses



The innate immune system enhances adaptive immune responses so they can be more effective.

Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The different modes of barrier defenses are associated with the external surfaces of the body, where pathogens may try to enter ([link]). The primary barrier to the entrance of microorganisms into the body is the skin. Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for bacteria in which to grow, but as these cells are continuously sloughed off from the skin, they carry bacteria and other pathogens with them. Additionally, sweat and other skin secretions may lower pH, contain toxic lipids, and physically wash microbes away.

Barrier Defenses				
Site	Specific defense	Protective aspect		
Skin	Epidermal surface	Keratinized cells of surface, Langerhans cells		
Skin (sweat/secretions)	Sweat glands, sebaceous glands	Low pH, washing action		
Oral cavity	Salivary glands	Lysozyme		
Stomach	Gastrointestinal tract	Low pH		
Mucosal surfaces	Mucosal epithelium	Nonkeratinized epithelial cells		
Normal flora (nonpathogenic bacteria)	Mucosal tissues	Prevent pathogens from growing on mucosal surfaces		

Another barrier is the saliva in the mouth, which is rich in lysozyme—an enzyme that destroys bacteria by digesting their cell walls. The acidic environment of the stomach, which is fatal to many pathogens, is also a barrier. Additionally, the mucus layer of the gastrointestinal tract, respiratory tract, reproductive tract, eyes, ears, and nose traps both microbes and debris, and facilitates their removal. In the case of the upper respiratory tract, ciliated epithelial cells move potentially contaminated mucus upwards to the mouth, where it is then swallowed into the digestive tract, ending up in the harsh acidic environment of the stomach. Considering how often you breathe compared to how often you eat or perform other activities that expose you to pathogens, it is not surprising that multiple barrier mechanisms have evolved to work in concert to protect this vital area.

Cells of the Innate Immune Response

A phagocyte is a cell that is able to surround and engulf a particle or cell, a process called **phagocytosis**. The phagocytes of the immune system engulf other particles or cells, either to clean an area of debris, old cells, or to kill pathogenic organisms such as bacteria. The phagocytes are the body's fast acting, first line of immunological defense against organisms that have breached barrier defenses and have entered the vulnerable tissues of the body.

Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a phagocytic ability, at least at some point during their life cycles. Phagocytosis is an important and effective mechanism of destroying pathogens during innate immune responses. The phagocyte takes the organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, the cause of tuberculosis, may be resistant to these enzymes and are therefore much more difficult to clear from the body. Macrophages, neutrophils, and dendritic cells are the major phagocytes of the immune system.

A macrophage is an irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body. Macrophages move through tissues and squeeze through capillary walls using pseudopodia. They not only participate in innate immune responses but have also evolved to cooperate with lymphocytes as part of the adaptive immune response. Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed within specific tissues such as lymph nodes. When pathogens breach the body's barrier defenses, macrophages are the first line of defense ([link]). They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lungs.

A **neutrophil** is a phagocytic cell that is attracted via chemotaxis from the bloodstream to infected tissues. These spherical cells are granulocytes. A granulocyte contains cytoplasmic granules, which in turn contain a variety of vasoactive mediators such as histamine. In contrast, macrophages are agranulocytes. An agranulocyte has few or no cytoplasmic granules. Whereas macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. Although, usually thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response, new

research has suggested that neutrophils play a role in the adaptive immune response as well, just as macrophages do.

A **monocyte** is a circulating precursor cell that differentiates into either a macrophage or dendritic cell, which can be rapidly attracted to areas of infection by signal molecules of inflammation.

Phagocytic Cells of the Innate Immune System					
Cell	Cell type	Primary location	Function in the innate immune response		
Macrophage	Agranulocyte	Body cavities/organs	Phagocytosis		
Neutrophil	Granulocyte	Blood	Phagocytosis		
Monocyte	Agranulocyte	Blood	Precursor of macrophage/dendritic cell		

Natural Killer Cells

NK cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses. NK cells recognize these cells by mechanisms that are still not well understood, but that presumably involve their surface receptors. NK cells can induce apoptosis, in which a cascade of events inside the cell causes its own death by either of two mechanisms:

1) NK cells are able to respond to chemical signals and express the fas ligand. The **fas ligand** is a surface molecule that binds to the fas molecule on the surface of the

infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it; or

2) The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. This increases the cells permeability to water and ions causing fluid to move into the cells resulting in lysis. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of pathogen-specific molecules, such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

These receptors, which are thought to have evolved prior to the adaptive immune response, are present on the cell surface whether they are needed or not. Their variety, however, is limited by two factors. First, the fact that each receptor type must be encoded by a specific gene requires the cell to allocate most or all of its DNA to make receptors able to recognize all pathogens. Secondly, the variety of receptors is limited by the finite surface area of the cell membrane. Thus, the innate immune system must "get by" using only a limited number of receptors that are active against as wide a variety of pathogens as possible. This strategy is in stark contrast to the approach used by the adaptive immune system, which uses large numbers of different receptors, each highly specific to a particular pathogen.

Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and initiate phagocytosis (or cellular apoptosis in the case of an intracellular pathogen) in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacterial components and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

Cytokines and Chemokines

A **cytokine** is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology. A **chemokine** is a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

Note:



Visit this <u>website</u> to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Early induced Proteins

Early induced proteins are those that are not constitutively present in the body, but are made as they are needed early during the innate immune response. **Interferons** are an example of early induced proteins. Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins. Thus, even though the initial cell is sacrificed, the surrounding cells are protected. Other early induced proteins specific for bacterial cell wall components are

mannose-binding protein and C-reactive protein, made in the liver, which bind specifically to polysaccharide components of the bacterial cell wall. Phagocytes such as macrophages have receptors for these proteins, and they are thus able to recognize them as they are bound to the bacteria. This brings the phagocyte and bacterium into close proximity and enhances the phagocytosis of the bacterium by the process known as opsonization. **Opsonization** is the tagging of a pathogen for phagocytosis by the binding of an antibody or an antimicrobial protein.

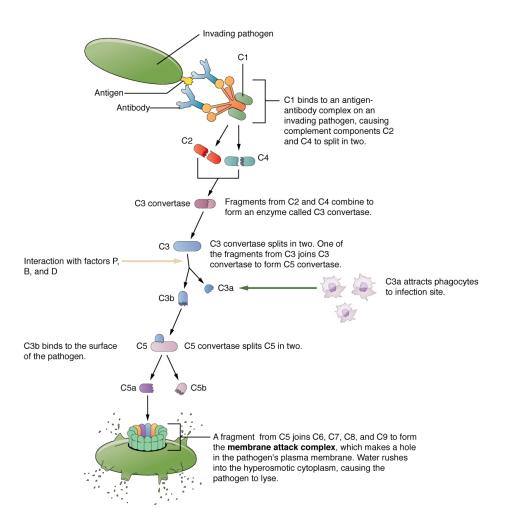
Complement System

The **complement** system is a series of proteins constitutively found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, even though they share features with some of the antibacterial proteins of this class. Made in the liver, they have a variety of functions in the innate immune response, using what is known as the "alternate pathway" of complement activation. Additionally, complement functions in the adaptive immune response as well, in what is called the classical pathway. The complement system consists of several proteins that enzymatically alter and fragment later proteins in a series, which is why it is termed cascade. Once activated, the series of reactions is irreversible, and releases fragments that have the following actions:

- Bind to the cell membrane of the pathogen that activates it, labeling it for phagocytosis (opsonization)
- Diffuse away from the pathogen and act as chemotactic agents to attract phagocytic cells to the site of inflammation
- Form damaging pores in the plasma membrane of the pathogen

[<u>link</u>] shows the classical pathway, which requires antibodies of the adaptive immune response. The alternate pathway does not require an antibody to become activated.

Complement Cascade and Function



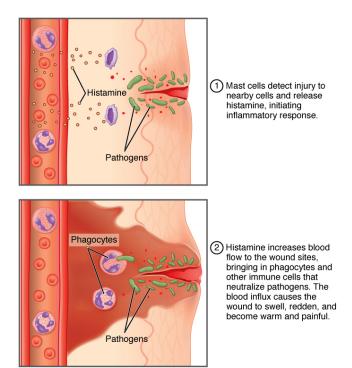
The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.

The splitting of the C3 protein is the common step to both pathways. In the alternate pathway, C3 is activated spontaneously and, after reacting with the molecules factor P, factor B, and factor D, splits apart. The larger fragment, C3b, binds to the surface of the pathogen and C3a, the smaller fragment, diffuses outward from the site of activation and attracts phagocytes to the site of infection. Surface-bound C3b then activates the rest of the cascade, with the last five proteins, C5–C9, forming the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic balance. The MAC is especially effective against a broad range of bacteria. The classical pathway is similar, except the early stages of activation require the presence of antibody bound to antigen, and thus is dependent on the adaptive immune response. The earlier fragments of the cascade

also have important functions. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by chemotactic attraction to smaller complement fragments. Additionally, once they arrive, their receptors for surface-bound C3b opsonize the pathogen for phagocytosis and destruction.

Inflammatory Response

The hallmark of the innate immune response is **inflammation**. Inflammation is something everyone has experienced. Stub a toe, cut a finger, or do any activity that causes tissue damage and inflammation will result, with its four characteristics: heat, redness, pain, and swelling ("loss of function" is sometimes mentioned as a fifth characteristic). It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in physical barriers that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair ([link]).



This reaction also brings in the cells of the innate immune system, allowing them to get rid of the sources of a possible infection. Inflammation is part of a very basic form of immune response. The process not only brings fluid and cells into the site to destroy the pathogen and remove it and debris from the site, but also helps to isolate the site, limiting the spread of the pathogen. Acute inflammation is a short-term inflammatory response to an insult to the body. If the cause of the inflammation is not resolved, however, it can lead to chronic inflammation, which is associated with major tissue destruction and fibrosis. Chronic inflammation is ongoing inflammation. It can be caused by foreign bodies, persistent pathogens, and autoimmune diseases such as rheumatoid arthritis.

There are four important parts to the inflammatory response:

- *Tissue Injury*. The released contents of injured cells stimulate the release of **mast cell** granules and their potent inflammatory mediators such as histamine, leukotrienes, and prostaglandins. **Histamine** increases the diameter of local blood vessels (vasodilation), causing an increase in blood flow. Histamine also increases the permeability of local capillaries, causing plasma to leak out and form interstitial fluid. This causes the swelling associated with inflammation. Additionally, injured cells, phagocytes, and basophils are sources of inflammatory mediators, including prostaglandins and leukotrienes. Leukotrienes attract neutrophils from the blood by chemotaxis and increase vascular permeability. Prostaglandins cause vasodilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen relieve pain by inhibiting prostaglandin production.
- *Vasodilation*. Many inflammatory mediators such as histamine are vasodilators that increase the diameters of local capillaries. This causes increased blood flow and is responsible for the heat and redness of inflamed tissue. It allows greater access of the blood to the site of inflammation.
- *Increased Vascular Permeability.* At the same time, inflammatory mediators increase the permeability of the local vasculature, causing leakage of fluid into the interstitial space, resulting in the swelling, or edema, associated with inflammation.
- *Recruitment of Phagocytes*. Leukotrienes are particularly good at attracting neutrophils from the blood to the site of infection by chemotaxis. Following an early neutrophil infiltrate stimulated by macrophage cytokines, more macrophages are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they phagocytose the pathogens and subsequently die, their accumulated cellular remains are visible as pus at the infection site.

Overall, inflammation is valuable for many reasons. Not only are the pathogens killed and debris removed, but the increase in vascular permeability encourages the entry of clotting factors, the first step towards wound repair. Inflammation also facilitates the transport of antigen to lymph nodes by dendritic cells for the development of the adaptive immune response.

Chapter Review

Innate immune responses are critical to the early control of infections. Whereas barrier defenses are the body's first line of physical defense against pathogens, innate immune responses are the first line of physiological defense. Innate responses occur rapidly, but with less specificity and effectiveness than the adaptive immune response. Innate responses can be caused by a variety of cells, mediators, and antibacterial proteins such as complement. Within the first few days of an infection, another series of antibacterial proteins are induced, each with activities against certain bacteria, including opsonization of certain species. Additionally, interferons are induced that protect cells from viruses in their vicinity. Finally, the innate immune response does not stop when the adaptive immune response is developed. In fact, both can cooperate and one can influence the other in their responses against pathogens.

Glossary

chemokine

soluble, long-range, cell-to-cell communication molecule

complement

enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria

cytokine

soluble, short-range, cell-to-cell communication molecule

early induced immune response

includes antimicrobial proteins stimulated during the first several days of an infection

fas ligand

molecule expressed on cytotoxic T cells and NK cells that binds to the fas molecule on a target cell and induces it do undergo apoptosis

granzyme

apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells

histamine

vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

inflammation

basic innate immune response characterized by heat, redness, pain, and swelling

interferons

early induced proteins made in virally infected cells that cause nearby cells to make antiviral proteins

macrophage

ameboid phagocyte found in several tissues throughout the body

mast cell

cell found in the skin and the lining of body cells that contains cytoplasmic granules with vasoactive mediators such as histamine

monocyte

precursor to macrophages and dendritic cells seen in the blood

neutrophil

phagocytic white blood cell recruited from the bloodstream to the site of infection via the bloodstream

opsonization

enhancement of phagocytosis by the binding of antibody or antimicrobial protein

pattern recognition receptor (PRR)

leukocyte receptor that binds to specific cell wall components of different bacterial species

perforin

molecule in NK cell and cytotoxic T cell granules that form pores in the membrane of a target cell

phagocytosis

movement of material from the outside to the inside of the cells via vesicles made from invaginations of the plasma membrane

OU Human Physiology: The Adaptive Immune Response: T lymphocytes and Their Functional Types By the end of this section, you will be able to:

- Explain the advantages of the adaptive immune response over the innate immune response
- Distinguish between the variable region domain and constant region domain of the T cell receptor in terms of function
- List the characteristics of an antigen
- Describe the process of antigen processing and presentation with respect to T cells
- Compare and contrast the two classes of MHC molecules
- Explain T cell tolerance testing
- Identify T cell types based on the presence of a CD4 or CD8 receptor
- Describe the process of clonal selection and T cell expansion in terms of destroying infected cells and producing memory cells
- Explain how a primary adaptive response prepares T cells for the secondary adaptive response
- Match the MHC class and affiliated cell type to the correct type of T cell, receptor (surface marker), and T cell response

Innate immune responses (and early induced responses) are in many cases ineffective at completely controlling pathogen growth. However, they slow pathogen growth and allow time for the adaptive immune response to strengthen and either control or eliminate the pathogen. The innate immune system also sends signals to the cells of the adaptive immune system, guiding them in how to attack the pathogen. Thus, these are the two important arms of the immune response.

The Benefits of the Adaptive Immune Response

The specificity of the adaptive immune response—its ability to specifically recognize and make a response against a wide variety of pathogens—is its great strength. Antigens, the small chemical groups often associated with pathogens, are recognized by receptors on the surface of B and T lymphocytes. The adaptive immune response to these antigens is so versatile that it can respond to nearly any pathogen. This increase in specificity comes because the adaptive immune response has a unique way to develop as many as 10^{11} , or 100 trillion, different receptors to recognize nearly every conceivable pathogen. How could so many different types of antibodies be encoded? And what about the many specificities of T cells? There is not nearly enough DNA in a cell to have a separate gene for each specificity. The mechanism was finally worked out in the 1970s and 1980s using the new tools of molecular genetics

Primary Disease and Immunological Memory

The immune system's first exposure to a pathogen is called a **primary adaptive response**. Symptoms of a first infection, called primary disease, are always relatively severe because it takes time for an initial adaptive immune response to a pathogen to become effective.

Upon re-exposure to the same pathogen, a secondary adaptive immune response is generated, which is stronger and faster that the primary response. The **secondary adaptive response** often eliminates a pathogen before it can cause significant tissue damage or any symptoms. Without symptoms, there is no disease, and the individual is not even aware of the infection. This secondary response is the basis of **immunological memory**, which protects us from getting diseases repeatedly from the same pathogen. By this mechanism, an individual's exposure to pathogens early in life spares the person from these diseases later in life.

Self Recognition

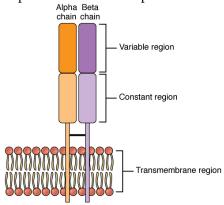
A third important feature of the adaptive immune response is its ability to distinguish between self-antigens, those that are normally present in the body, and foreign antigens, those that might be on a potential pathogen. As T and B cells mature, there are mechanisms in place that prevent them from recognizing self-antigen, preventing a damaging immune response against the body. These mechanisms are not 100 percent effective, however, and their breakdown leads to autoimmune diseases, which will be discussed later in this chapter.

T Cell-Mediated Immune Responses

The primary cells that control the adaptive immune response are the lymphocytes, the T and B cells. T cells are particularly important, as they not only control a multitude of immune responses directly, but also control B cell immune responses in many cases as well. Thus, many of the decisions about how to attack a pathogen are made at the T cell level, and knowledge of their functional types is crucial to understanding the functioning and regulation of adaptive immune responses as a whole.

T lymphocytes recognize antigens based on a two-chain protein receptor. The most common and important of these are the alpha-beta T cell receptors ([link]).





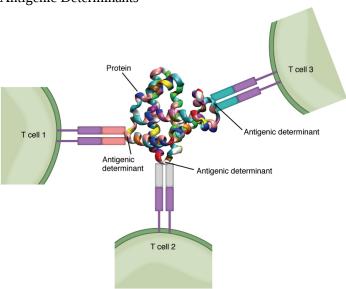
Notice the constant and variable regions of each chain, anchored by the transmembrane region.

There are two chains in the T cell receptor, and each chain consists of two domains. The **variable region domain** is furthest away from the T cell membrane and is so named because its amino acid sequence varies between receptors. In contrast, the **constant region domain** has less variation. The differences in the amino acid sequences of the variable domains are the molecular basis of the diversity of antigens the receptor can recognize. Thus, the antigen-binding site of the receptor consists of the terminal ends of both receptor chains, and the amino acid sequences of those two areas combine to determine its antigenic specificity. Each T cell produces only one type of receptor and thus is specific for a single particular antigen.

Antigens

Antigens on pathogens are usually large and complex, and consist of many antigenic determinants. An **antigenic determinant** (also called, **epitope**) is one of the small regions within an antigen to which a receptor can bind, and antigenic determinants are limited by the size of the receptor itself. They usually consist of six or fewer amino acid residues in a protein, or one or two sugar moieties in a carbohydrate antigen. Antigenic determinants on a carbohydrate antigen are usually less diverse than on a protein antigen. Carbohydrate antigens are found on bacterial cell walls and on red blood cells (the ABO blood group antigens). Protein antigens are complex because of the variety of three-dimensional shapes that proteins can assume, and are especially important for the immune responses to viruses and worm parasites. It is the interaction of the shape of the antigen and the complementary shape of the amino acids of the antigen-binding site that accounts for the chemical basis of specificity ([link]).

Antigenic Determinants

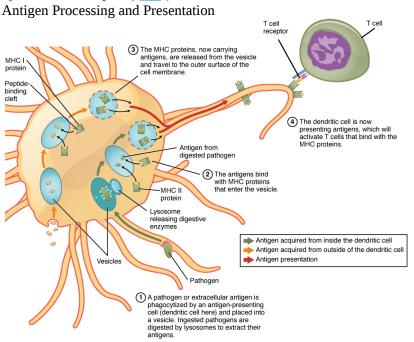


A typical protein antigen has multiple antigenic determinants, shown by the ability of T cells with three different specificities to bind to different parts of the same antigen.

Antigen Processing and Presentation

Although [link] shows T cell receptors interacting with antigenic determinants directly, the mechanism that T cells use to recognize antigens is, in reality, much more complex. T cells do not recognize free-floating or cell-bound antigens as they appear on the surface of the pathogen. They only recognize antigen on the surface of specialized cells called antigen-presenting cells. Antigens are internalized by these cells. **Antigen processing** is a mechanism that enzymatically cleaves the antigen into smaller pieces. The antigen fragments are then brought to the cell's surface and associated with a specialized type of antigen-presenting glycoprotein known as a **major histocompatibility complex (MHC)** molecule. The MHC is the cluster of genes that encode these antigen-presenting molecules. The association of the antigen fragments with an MHC molecule on the surface of a cell is known as **antigen presentation** and results in the recognition of antigen by a T cell. This association of antigen and MHC occurs inside the cell, and it is the complex of the two that is brought to the surface. The peptide-binding cleft is a small indentation at the end of the MHC molecule that is furthest away from the cell membrane; it is here that

the processed fragment of antigen sits. MHC molecules are capable of presenting a variety of antigens, depending on the amino acid sequence, in their peptide-binding clefts. It is the combination of the MHC molecule and the fragment of the original peptide or carbohydrate that is actually physically recognized by the T cell receptor ([link]).



Two distinct types of MHC molecules, **MHC class I** and **MHC class II**, play roles in antigen presentation. Although produced from different genes, they both have similar functions. They bring processed antigen to the surface of the cell via a transport vesicle and present the antigen to the T cell and its receptor. Antigens from different classes of pathogens, however, use different MHC classes and take different routes through the cell to get to the surface for presentation. The basic mechanism, though, is the same. Antigens are processed by digestion, are brought into the endomembrane system of the cell, and then are expressed on the surface of the antigen-presenting cell for antigen recognition by a T cell. Intracellular antigens are typical of viruses, which replicate inside the cell, and certain other intracellular parasites and bacteria. These antigens are processed in the cytosol by an enzyme complex known as the proteasome and are then brought into the endoplasmic reticulum by the transporter associated with antigen processing (TAP) system, where they interact with class I MHC molecules and are eventually transported to the cell surface by a transport vesicle.

Extracellular antigens, characteristic of many bacteria, parasites, and fungi that do not replicate inside the cell's cytoplasm, are brought into the endomembrane system of the cell by receptor-mediated endocytosis. The resulting vesicle fuses with vesicles from the Golgi complex, which contain pre-formed MHC class II molecules. After fusion of these two vesicles and the association of antigen and MHC, the new vesicle makes its way to the cell surface.

Professional Antigen-presenting Cells

Nucleated cell types express class I molecules for the presentation of intracellular antigens. Class I MHC molecules are only recognized by cytotoxic T-cells. When a class I is bound by a cytotoxic T cell this will stimulate a cytotoxic T cell immune response, eventually destroying the cell and the pathogen within. This is especially important when it comes to the most common class of intracellular pathogens,

the virus. Viruses infect nearly every tissue of the body, so all these tissues must necessarily be able to express class I MHC or no T cell response can be made.

On the other hand, class II MHC molecules are expressed only on the cells of the immune system, specifically cells that affect other arms of the immune response. Thus, these cells are called "professional" antigen-presenting cells to distinguish them from those that bear class I MHC. The three types of professional antigen presenters are macrophages, dendritic cells, and B cells ([link]).

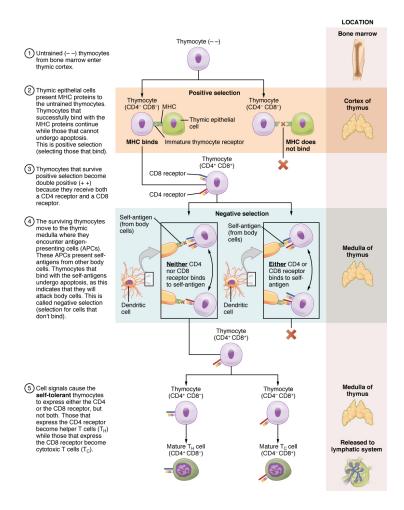
Macrophages stimulate T cells to release cytokines that enhance phagocytosis. Dendritic cells also kill pathogens by phagocytosis (see [link]), but their major function is to bring antigens to regional draining lymph nodes. The lymph nodes are the locations in which most T cell responses against pathogens of the interstitial tissues are mounted. Macrophages are found in the skin and in the lining of mucosal surfaces, such as the nasopharynx, stomach, lungs, and intestines. B cells may also present antigens to T cells, which are necessary for certain types of antibody responses, to be covered later in this chapter.

Classes of Antigen-presenting Cells				
МНС	Cell type	Phagocytic?	Function	
Class I	Nucleated	No	Stimulates cytotoxic T cell immune response	
Class II	Macrophage	Yes	Stimulates phagocytosis and presentation at primary infection site	
Class II	Dendritic	Yes, in tissues	Brings antigens to regional lymph nodes	
Class II	B cell	Yes, internalizes surface Ig and antigen	Stimulates antibody secretion by B cells	

T Cell Development and Differentiation

The process of eliminating T cells that might attack the cells of one's own body is referred to as **T cell tolerance**. While thymocytes are in the cortex of the thymus, they are referred to as "double negatives," meaning that they do not bear the CD4 or CD8 molecules that you can use to follow their pathways of differentiation ([link]). In the cortex of the thymus, they are exposed to cortical epithelial cells. In a process known as **positive selection**, double-negative thymocytes bind to the MHC molecules they observe on the thymic epithelia, and the MHC molecules of "self" are selected. This mechanism kills many thymocytes during T cell differentiation. In fact, only two percent of the thymocytes that enter the thymus leave it as mature, functional T cells.

Differentiation of T Cells within the Thymus



Thymocytes enter the thymus and go through a series of developmental stages that ensures both function and tolerance before they leave and become functional components of the adaptive immune response.

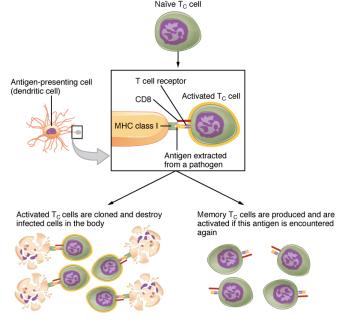
Later, the cells become double positives that express both CD4 and CD8 markers and move from the cortex to the junction between the cortex and medulla. It is here that negative selection takes place. In **negative selection**, self-antigens are brought into the thymus from other parts of the body by professional antigen-presenting cells. The T cells that bind to these self-antigens are selected for negatively and are killed by apoptosis. In summary, the only T cells left are those that can bind to MHC molecules of the body with foreign antigens presented on their binding clefts, preventing an attack on one's own body tissues, at least under normal circumstances. Tolerance can be broken, however, by the development of an autoimmune response, to be discussed later in this chapter.

The cells that leave the thymus become single positives, expressing either CD4 or CD8, but not both (see [link]). The CD4⁺ T cells will bind to class II MHC and the CD8⁺ cells will bind to class I MHC. The discussion that follows explains the functions of these molecules and how they can be used to differentiate between the different T cell functional types.

Mechanisms of T Cell-mediated Immune Responses

Mature T cells become activated by recognizing processed foreign antigen in association with a self-MHC molecule and begin dividing rapidly by mitosis. This proliferation of T cells is called **clonal expansion** and is necessary to make the immune response strong enough to effectively control a pathogen. How does the body select only those T cells that are needed against a specific pathogen? Again, the specificity of a T cell is based on the amino acid sequence and the three-dimensional shape of the antigen-binding site formed by the variable regions of the two chains of the T cell receptor ([link]). **Clonal selection** is the process of antigen binding only to those T cells that have receptors specific to that antigen. Each T cell that is activated has a specific receptor "hard-wired" into its DNA, and all of its progeny will have identical DNA and T cell receptors, forming clones of the original T cell.

Clonal Selection and Expansion of T Lymphocytes



Stem cells differentiate into T cells with specific receptors, called clones. The clones with receptors specific for antigens on the pathogen are selected for and expanded.

Clonal Selection and Expansion

The clonal selection theory was proposed by Frank Burnet in the 1950s. However, the term clonal selection is not a complete description of the theory, as clonal expansion goes hand in glove with the selection process. The main tenet of the theory is that a typical individual has a multitude (10^{11}) of different types of T cell clones based on their receptors. In this use, a **clone** is a group of lymphocytes that share the same **antigen receptor**. Each clone is necessarily present in the body in low numbers. Otherwise, the body would not have room for lymphocytes with so many specificities.

Only those clones of lymphocytes whose receptors are activated by the antigen are stimulated to proliferate. Keep in mind that most antigens have multiple antigenic determinants, so a T cell response to a typical antigen involves a polyclonal response. A **polyclonal response** is the stimulation of multiple T cell clones. Once activated, the selected clones increase in number and make many copies of each cell

type, each clone with its unique receptor. By the time this process is complete, the body will have large numbers of specific lymphocytes available to fight the infection (see [link]).

The Cellular Basis of Immunological Memory

As already discussed, one of the major features of an adaptive immune response is the development of immunological memory.

During a primary adaptive immune response, both **memory T cells** and **effector T cells** are generated. Memory T cells are long-lived and can even persist for a lifetime. Memory cells are primed to act rapidly. Thus, any subsequent exposure to the pathogen will elicit a very rapid T cell response. This rapid, secondary adaptive response generates large numbers of effector T cells so fast that the pathogen is often overwhelmed before it can cause any symptoms of disease. This is what is meant by immunity to a disease. The same pattern of primary and secondary immune responses occurs in B cells and the antibody response, as will be discussed later in the chapter.

T Cell Types and their Functions

In the discussion of T cell development, you saw that mature T cells express either the CD4 marker or the CD8 marker, but not both. These markers are cell adhesion molecules that keep the T cell in close contact with the antigen-presenting cell by directly binding to the MHC molecule (to a different part of the molecule than does the antigen). Thus, T cells and antigen-presenting cells are held together in two ways: by CD4 or CD8 attaching to MHC and by the T cell receptor binding to antigen ([link]).

Pathogen Presentation Antigen-presenting cell (dendritic cell) Helper T cells release cytokines that activate much of the adaptive and nonadaptive immune system during infection (a) CD4 Activated T_H cell Antigen Cytotoxic T cells destroy infected cells by releasing enzymes that rupture cell membranes (b) MHC I Activated T_C cell Granzymes Helper T cell receptor Perforins T cell receptor

(a) CD4 is associated with helper and regulatory T cells. An extracellular pathogen is processed and presented in the binding cleft of a class II MHC molecule, and this interaction is strengthened by the CD4 molecule. (b) CD8 is associated with cytotoxic T cells. An intracellular pathogen is presented by

a class I MHC molecule, and CD8 interacts with it

Although the correlation is not 100 percent, CD4-bearing T cells are associated with helper functions and CD8-bearing T cells are associated with cytotoxicity. These functional distinctions based on CD4 and CD8 markers are useful in defining the function of each type.

Helper T Cells and their Cytokines

Helper T cells (Th), bearing the CD4 molecule, function by secreting cytokines that act to enhance other immune responses. There are two classes of Th cells, and they act on different components of the immune response. These cells are not distinguished by their surface molecules but by the characteristic set of cytokines they secrete ([link]).

Th1 cells are a type of helper T cell that secretes cytokines that regulate the immunological activity and development of a variety of cells, including macrophages and other types of T cells.

Th2 cells, on the other hand, are cytokine-secreting cells that act on B cells to drive their differentiation into plasma cells that make antibody. In fact, T cell help is required for antibody responses to most protein antigens, and these are called T cell-dependent antigens.

Cytotoxic T cells

Cytotoxic T cells (Tc) are T cells that kill target cells by inducing apoptosis using the same mechanism as NK cells. They either express Fas ligand, which binds to the fas molecule on the target cell, or act by using perforins and granzymes contained in their cytoplasmic granules. As was discussed earlier with NK cells, killing a virally infected cell before the virus can complete its replication cycle results in the production of no infectious particles. As more Tc cells are developed during an immune response, they overwhelm the ability of the virus to cause disease. In addition, each Tc cell can kill more than one target cell, making them especially effective. Tc cells are so important in the antiviral immune response that some speculate that this was the main reason the adaptive immune response evolved in the first place.

Regulatory T Cells

Regulatory T cells (Treg), or suppressor T cells, are the most recently discovered of the types listed here, so less is understood about them. In addition to CD4, they bear the molecules CD25 and FOXP3. Exactly how they function is still under investigation, but it is known that they suppress other T cell immune responses. This is an important feature of the immune response, because if clonal expansion during immune responses were allowed to continue uncontrolled, these responses could lead to autoimmune diseases and other medical issues.

Not only do T cells directly destroy pathogens, but they regulate nearly all other types of the adaptive immune response as well, as evidenced by the functions of the T cell types, their surface markers, the cells they work on, and the types of pathogens they work against (see [link]).

Functi	Functions of T Cell Types and Their Cytokines								
T cell	Main target	Function	Pathogen	Surface marker	МНС	Cytokines or mediators			
Tc	Infected cells	Cytotoxicity	Intracellular	CD8	Class I	Perforins, granzymes, and fas ligand			
Th1	Macrophage	Helper inducer	Extracellular	CD4	Class II	Interferon- γ and TGF-β			
Th2	B cell	Helper inducer	Extracellular	CD4	Class II	IL-4, IL-6, IL-10, and others			
Treg	Th cell	Suppressor	None	CD4, CD25	;	TGF-β and IL-10			

Chapter Review

T cells recognize antigens with their antigen receptor, a complex of two protein chains on their surface. They do not recognize self-antigens, however, but only processed antigen presented on their surfaces in a binding groove of a major histocompatibility complex molecule. T cells develop in the thymus, where they learn to use self-MHC molecules to recognize only foreign antigens, thus making them tolerant to self-antigens. There are several functional types of T lymphocytes, the major ones being helper, regulatory, and cytotoxic T cells.

Glossary

antigenic determinant

(also called, epitope) one of the chemical groups recognized by a single type of lymphocyte antigen receptor

antigen presentation

binding of processed antigen to the protein-binding cleft of a major histocompatibility complex molecule

antigen processing

internalization and digestion of antigen in an antigen-presenting cell

antigen receptor

two-chain receptor by which lymphocytes recognize antigen

clone

group of lymphocytes sharing the same antigen receptor

clonal expansion

growth of a clone of selected lymphocytes

clonal selection

stimulating growth of lymphocytes that have specific receptors

constant region domain

part of a lymphocyte antigen receptor that does not vary much between different receptor types

cytotoxic T cells (Tc)

T lymphocytes with the ability to induce apoptosis in target cells

effector T cells

immune cells with a direct, adverse effect on a pathogen

helper T cells (Th)

T cells that secrete cytokines to enhance other immune responses, involved in activation of both B and T cell lymphocytes

immunological memory

ability of the adaptive immune response to mount a stronger and faster immune response upon reexposure to a pathogen

major histocompatibility complex (MHC)

gene cluster whose proteins present antigens to T cells

memory T cells

long-lived immune cell reserved for future exposure to an pathogen

MHC class I

found on most cells of the body, it binds to the CD8 molecule on T cells

MHC class II

found on macrophages, dendritic cells, and B cells, it binds to CD4 molecules on T cells

negative selection

selection against thymocytes in the thymus that react with self-antigen

polyclonal response

response by multiple clones to a complex antigen with many determinants

primary adaptive response

immune system's response to the first exposure to a pathogen

positive selection

selection of thymocytes within the thymus that interact with self, but not non-self, MHC molecules

regulatory T cells (Treg)

(also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

secondary adaptive response

immune response observed upon re-exposure to a pathogen, which is stronger and faster than a primary response

T cell tolerance

process during T cell differentiation where most T cells that recognize antigens from one's own body are destroyed

Th1 cells

cells that secrete cytokines that enhance the activity of macrophages and other cells

Th2 cells

cells that secrete cytokines that induce B cells to differentiate into antibody-secreting plasma cells

variable region domain

part of a lymphocyte antigen receptor that varies considerably between different receptor types

OU Human Physiology: The Adaptive Immune Response: B-lymphocytes and Antibodies

By the end of this section, you will be able to:

- Summarize the location of B cell maturation and tolerance
- Explain the structural properties of an antibody
- Relate the B cell receptor to an antibody in terms of structure and function
- Describe the process of clonal selection in B cells
- Explain how a primary adaptive response prepares B cells for the secondary adaptive response
- Compare and contrast passive and active naturally acquired and artificially acquired immunity

Antibodies were the first component of the adaptive immune response to be characterized by scientists working on the immune system. It was already known that individuals who survived a bacterial infection were immune to re-infection with the same pathogen. Early microbiologists took serum from an immune patient and mixed it with a fresh culture of the same type of bacteria, then observed the bacteria under a microscope. The bacteria became clumped in a process called agglutination. When a different bacterial species was used, the agglutination did not happen. Thus, there was something in the serum of immune individuals that could specifically bind to and agglutinate bacteria.

Scientists now know the cause of the agglutination is an antibody molecule, also called an **immunoglobulin**. What is an antibody? An antibody protein is essentially a secreted form of a B cell receptor. (In fact, surface immunoglobulin is another name for the B cell receptor.) Not surprisingly, the same genes encode both the secreted antibodies and the surface immunoglobulins. One minor difference in the way these proteins are synthesized distinguishes a naïve B cell with antibody on its surface from an antibody-secreting plasma cell with no antibodies on its surface. The antibodies of the plasma cell have the exact same antigen-binding site and specificity as their B cell precursors.

There are five different classes of antibody found in humans: IgM, IgD, IgG, IgA, and IgE. Each of these has specific functions in the immune

response, so by learning about them, researchers can learn about the great variety of antibody functions critical to many adaptive immune responses.

B cells do not recognize antigen in the complex fashion of T cells. B cells can recognize native, unprocessed antigen and do not require the participation of MHC molecules and antigen-presenting cells.

B Cell Differentiation and Activation

B cells differentiate in the bone marrow. During the process of maturation, up to 100 trillion different clones of B cells are generated, which is similar to the diversity of antigen receptors seen in T cells.

B cell differentiation and the development of tolerance are not quite as well understood as it is in T cells. **Central tolerance** is the destruction or inactivation of B cells that recognize self-antigens in the bone marrow, and its role is critical and well established. In the process of **clonal deletion**, immature B cells that bind strongly to self-antigens expressed on tissues are signaled to commit suicide by apoptosis, removing them from the population. In the process of **clonal anergy**, however, B cells exposed to soluble antigen in the bone marrow are not physically deleted, but become unable to function.

Another mechanism called peripheral tolerance is a direct result of T cell tolerance. In **peripheral tolerance**, functional, mature B cells leave the bone marrow but have yet to be exposed to self-antigen. Most protein antigens require signals from helper T cells (Th2) to proceed to make antibody. When a B cell binds to a self-antigen but receives no signals from a nearby Th2 cell to produce antibody, the cell is signaled to undergo apoptosis and is destroyed. This is yet another example of the control that T cells have over the adaptive immune response.

After B cells are activated by their binding to antigen, they differentiate into plasma cells. Plasma cells often leave the secondary lymphoid organs, where the response is generated, and migrate back to the bone marrow, where the whole differentiation process started. After secreting antibodies for a specific period, they die, as most of their energy is devoted to making

antibodies and not to maintaining themselves. Thus, plasma cells are said to be terminally differentiated.

The final B cell of interest is the memory B cell, which results from the clonal expansion of an activated B cell. Memory B cells function in a way similar to memory T cells. They lead to a stronger and faster secondary response when compared to the primary response, as illustrated below.

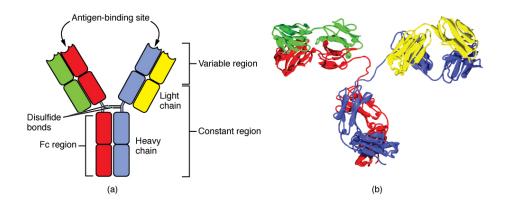
Antibody Structure

Antibodies are glycoproteins consisting of two types of polypeptide chains with attached carbohydrates. The **heavy chain** and the **light chain** are the two polypeptides that form the antibody. The main differences between the classes of antibodies are in the differences between their heavy chains, but as you shall see, the light chains have an important role, forming part of the antigen-binding site on the antibody molecules.

Four-chain Models of Antibody Structures

All antibody molecules have two identical heavy chains and two identical light chains. (Some antibodies contain multiple units of this four-chain structure.) The **Fc region** of the antibody is formed by the two heavy chains coming together, usually linked by disulfide bonds ([link]). The Fc portion of the antibody is important in that many effector cells of the immune system have Fc receptors. Cells having these receptors can then bind to antibody-coated pathogens, greatly increasing the specificity of the effector cells. At the other end of the molecule are two identical antigen-binding sites.

Antibody and IgG2 Structures



The typical four chain structure of a generic antibody (a) and the corresponding three-dimensional structure of the antibody IgG2 (b). (credit b: modification of work by Tim Vickers)

Five Classes of Antibodies and their Functions

In general, antibodies have two basic functions. They can act as the B cell antigen receptor or they can be secreted, circulate, and bind to a pathogen, often labeling it for identification by other forms of the immune response. Of the five antibody classes, notice that only two can function as the antigen receptor for naïve B cells: IgM and IgD ([link]). Mature B cells that leave the bone marrow express both IgM and IgD, but both antibodies have the same antigen specificity. Only IgM is secreted, however, and no other nonreceptor function for IgD has been discovered.

Five Classes of Antibodies

The Five Immunoglobulin (Ig) Classes								
	lgM pentamer	IgG monomer	Secretory IgA dimer	lgE monomer	lgD monomer			
			Secretory component					
Heavy chains	μ	γ	α	ε	δ			
Number of antigen binding sites	10	2	4	2	2			
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000			
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%			
Crosses placenta	no	yes	no	no	no			
Fixes complement	yes	yes	no	no	no			
Fc binds to		phagocytes		mast cells and basophils				
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor			

IgM consists of five four-chain structures (20 total chains with 10 identical antigen-binding sites) and is thus the largest of the antibody molecules. IgM is usually the first antibody made during a primary response. Its 10 antigen-binding sites and large shape allow it to bind well to many bacterial surfaces. It is excellent at binding complement proteins and activating the complement cascade, consistent with its role in promoting chemotaxis, opsonization, and cell lysis. Thus, it is a very effective antibody against bacteria at early stages of a primary antibody response. As the primary response proceeds, the antibody produced in a B cell can change to IgG, IgA, or IgE by the process known as class switching. **Class switching** is the change of one antibody class to another. While the class of antibody changes, the specificity and the antigen-binding sites do not. Thus, the antibodies made are still specific to the pathogen that stimulated the initial IgM response.

IgG is a major antibody of late primary responses and the main antibody of secondary responses in the blood. This is because class switching occurs

during primary responses. IgG is a monomeric antibody that clears pathogens from the blood and can activate complement proteins (although not as well as IgM), taking advantage of its antibacterial activities. Furthermore, this class of antibody is the one that crosses the placenta to protect the developing fetus from disease exits the blood to the interstitial fluid to fight extracellular pathogens.

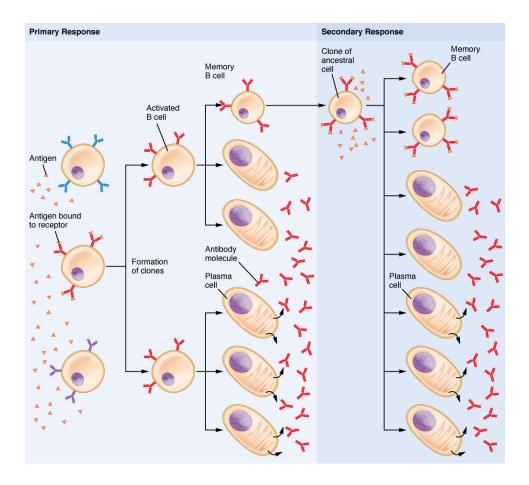
IgA exists in two forms, a four-chain monomer in the blood and an eight-chain structure, or dimer, in exocrine gland secretions of the mucous membranes, including mucus, saliva, and tears. Thus, dimeric IgA is the only antibody to leave the interior of the body to protect body surfaces. IgA is also of importance to newborns, because this antibody is present in mother's breast milk (colostrum), which serves to protect the infant from disease.

IgE is usually associated with allergies and anaphylaxis. It is present in the lowest concentration in the blood, because its Fc region binds strongly to an IgE-specific Fc receptor on the surfaces of mast cells. IgE makes mast cell degranulation very specific, such that if a person is allergic to peanuts, there will be peanut-specific IgE bound to his or her mast cells. In this person, eating peanuts will cause the mast cells to degranulate, sometimes causing severe allergic reactions, including anaphylaxis, a severe, systemic allergic response that can cause death.

Clonal Selection of B Cells

Clonal selection and expansion work much the same way in B cells as in T cells. Only B cells with appropriate antigen specificity are selected for and expanded ([link]). Eventually, the plasma cells secrete antibodies with antigenic specificity identical to those that were on the surfaces of the selected B cells. Notice in the figure that both plasma cells and memory B cells are generated simultaneously.

Clonal Selection of B Cells



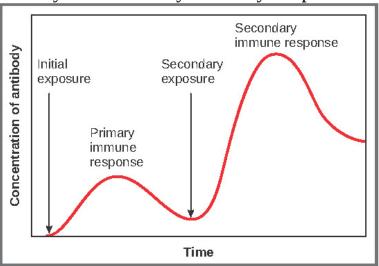
During a primary B cell immune response, both antibody-secreting plasma cells and memory B cells are produced. These memory cells lead to the differentiation of more plasma cells and memory B cells during secondary responses.

Primary versus Secondary B Cell Responses

Primary and secondary responses as they relate to T cells were discussed earlier. This section will look at these responses with B cells and antibody production. Because antibodies are easily obtained from blood samples, they are easy to follow and graph ([link]). As you will see from the figure, the primary response to an antigen (representing a pathogen) is delayed by

several days. This is the time it takes for the B cell clones to expand and differentiate into plasma cells. The level of antibody produced is low, but it is sufficient for immune protection. The second time a person encounters the same antigen, there is no time delay, and the amount of antibody made is much higher. Thus, the secondary antibody response overwhelms the pathogens quickly and, in most situations, no symptoms are felt. When a different antigen is used, another primary response is made with its low antibody levels and time delay.

Primary and Secondary Antibody Responses



Antigen A is given once to generate a primary response and later to generate a secondary response. When a different antigen is given for the first time, a new primary response is made.

Active versus Passive Immunity

Immunity to pathogens, and the ability to control pathogen growth so that damage to the tissues of the body is limited, can be acquired by (1) the active development of an immune response in the infected individual or (2) the passive transfer of immune components from an immune individual to a

nonimmune one. Both active and passive immunity have examples in the natural world and as part of medicine.

Active immunity is the resistance to pathogens acquired during an adaptive immune response within an individual ([link]). Naturally acquired active immunity, the response to a pathogen, is the focus of this chapter. Artificially acquired active immunity involves the use of vaccines. A vaccine is a killed or weakened pathogen or its components that, when administered to a healthy individual, leads to the development of immunological memory (a weakened primary immune response) without causing much in the way of symptoms. Thus, with the use of vaccines, one can avoid the damage from disease that results from the first exposure to the pathogen, yet reap the benefits of protection from immunological memory. The advent of vaccines was one of the major medical advances of the twentieth century and led to the eradication of smallpox and the control of many infectious diseases, including polio, measles, and whooping cough.

Active versus Passive Immunity					
	Natural	Artificial			
Active	Adaptive immune response	Vaccine response			
Passive	Trans-placental antibodies/breastfeeding	Immune globulin injections			

Passive immunity arises from the transfer of antibodies to an individual without requiring them to mount their own active immune response. Naturally acquired passive immunity is seen during fetal development. IgG is transferred from the maternal circulation to the fetus via the placenta, protecting the fetus from infection and protecting the newborn for the first few months of its life. As already stated, a newborn benefits from the IgA

antibodies it obtains from milk during breastfeeding. The fetus and newborn thus benefit from the immunological memory of the mother to the pathogens to which she has been exposed. In medicine, artificially acquired passive immunity usually involves injections of immunoglobulins, taken from animals previously exposed to a specific pathogen. This treatment is a fast-acting method of temporarily protecting an individual who was possibly exposed to a pathogen. The downside to both types of passive immunity is the lack of the development of immunological memory. Once the antibodies are transferred, they are effective for only a limited time before they degrade.

Note:



Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this <u>video</u> to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

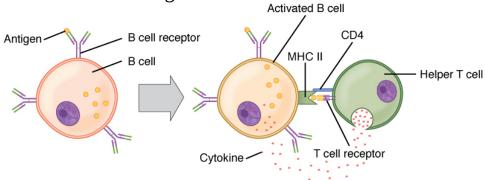
T cell-dependent versus T cell-independent Antigens

As discussed previously, Th2 cells secrete cytokines that drive the production of antibodies in a B cell, responding to complex antigens such as those made by proteins. On the other hand, some antigens are T cell independent. A **T cell-independent antigen** usually is in the form of repeated carbohydrate moieties found on the cell walls of bacteria. Each antibody on the B cell surface has two binding sites, and the repeated nature of T cell-independent antigen leads to crosslinking of the surface antibodies

on the B cell. The crosslinking is enough to activate it in the absence of T cell cytokines.

A **T** cell-dependent antigen, on the other hand, usually is not repeated to the same degree on the pathogen and thus does not crosslink surface antibody with the same efficiency. To elicit a response to such antigens, the B and T cells must come close together ([link]). The B cell must receive two signals to become activated. Its surface immunoglobulin must recognize native antigen. Some of this antigen is internalized, processed, and presented to the Th2 cells on a class II MHC molecule. The T cell then binds using its antigen receptor and is activated to secrete cytokines that diffuse to the B cell, finally activating it completely. Thus, the B cell receives signals from both its surface antibody and the T cell via its cytokines, and acts as a professional antigen-presenting cell in the process.

T and B Cell Binding



To elicit a response to a T cell-dependent antigen, the B and T cells must come close together. To become fully activated, the B cell must receive two signals from the native antigen and the T cell's cytokines.



Visit this <u>website</u> to learn more about the adaptive immune response. What is the role of the dendritic cell in an HIV infection?

Chapter Review

B cells, which develop within the bone marrow, are responsible for making five different classes of antibodies, each with its own functions. B cells have their own mechanisms for tolerance, but in peripheral tolerance, the B cells that leave the bone marrow remain inactive due to T cell tolerance. Some B cells do not need T cell cytokines to make antibody, and they bypass this need by the crosslinking of their surface immunoglobulin by repeated carbohydrate residues found in the cell walls of many bacterial species. Others require T cells to become activated.

Glossary

active immunity

immunity developed from an individual's own immune system

central tolerance

B cell tolerance induced in immature B cells of the bone marrow

class switching

ability of B cells to change the class of antibody they produce without altering the specificity for antigen

clonal anergy

process whereby B cells that react to soluble antigens in bone marrow are made nonfunctional

clonal deletion

removal of self-reactive B cells by inducing apoptosis

Fc region

in an antibody molecule, the site where the two termini of the heavy chains come together; many cells have receptors for this portion of the antibody, adding functionality to these molecules

heavy chain

larger protein chain of an antibody

IgA

antibody whose dimer is secreted by exocrine glands, is especially effective against digestive and respiratory pathogens, and can pass immunity to an infant through breastfeeding

IgD

class of antibody whose only known function is as a receptor on naive B cells; important in B cell activation

IgE

antibody that binds to mast cells and causes antigen-specific degranulation during an allergic response

IgG

main blood antibody of late primary and early secondary responses; passed from mother to unborn child via placenta

IgM

antibody whose monomer is a surface receptor of naive B cells; the pentamer is the first antibody made blood plasma during primary responses

immunoglobulin

protein antibody; occurs as one of five main classes

light chain

small protein chain of an antibody

passive immunity

transfer of immunity to a pathogen to an individual that lacks immunity to this pathogen usually by the injection of antibodies

peripheral tolerance

mature B cell made tolerant by lack of T cell help

T cell-dependent antigen antigen that binds to B cells, which requires signals from T cells to make antibody

T cell-independent antigen binds to B cells, which do not require signals from T cells to make antibody

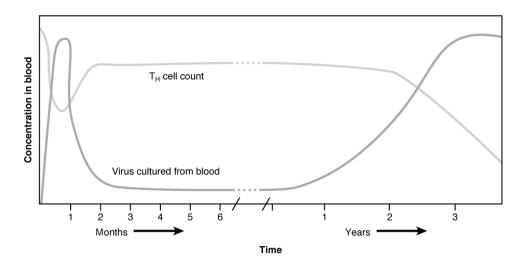
OU Human Physiology: The Immune Response against Pathogens By the end of this section, you will be able to:

- Explain the development of immunological competence
- Describe the mucosal immune response
- Discuss immune responses against bacterial, viral, fungal, and animal pathogens
- Describe different ways pathogens evade immune responses

Now that you understand the development of mature, naïve B cells and T cells, and some of their major functions, how do all of these various cells, proteins, and cytokines come together to actually resolve an infection? Ideally, the immune response will rid the body of a pathogen entirely. The adaptive immune response, with its rapid clonal expansion, is well suited to this purpose. Think of a primary infection as a race between the pathogen and the immune system. The pathogen bypasses barrier defenses and starts multiplying in the host's body. During the first 4 to 5 days, the innate immune response will partially control, but not stop, pathogen growth. As the adaptive immune response gears up, however, it will begin to clear the pathogen from the body, while at the same time becoming stronger and stronger. When following antibody responses in patients with a particular disease such as a virus, this clearance is referred to as seroconversion (sero-= "serum"). **Seroconversion** is the reciprocal relationship between virus levels in the blood and antibody levels. As the antibody levels rise, the virus levels decline, and this is a sign that the immune response is being at least partially effective (partially, because in many diseases, seroconversion does not necessarily mean a patient is getting well).

An excellent example of this is seroconversion during HIV disease ([link]). Notice that antibodies are made early in this disease, and the increase in anti-HIV antibodies correlates with a decrease in detectable virus in the blood. Although these antibodies are an important marker for diagnosing the disease, they are not sufficient to completely clear the virus. Several years later, the vast majority of these individuals, if untreated, will lose their entire adaptive immune response, including the ability to make antibodies, during the final stages of AIDS.

HIV Disease Progression



Seroconversion, the rise of anti-HIV antibody levels and the concomitant decline in measurable virus levels, happens during the first several months of HIV disease. Unfortunately, this antibody response is ineffective at controlling the disease, as seen by the progression of the disease towards AIDS, in which all adaptive immune responses are compromised.

Note:

Everyday Connection

Disinfectants: Fighting the Good Fight?

"Wash your hands!" Parents have been telling their children this for generations. Dirty hands can spread disease. But is it possible to get rid of enough pathogens that children will never get sick? Are children who avoid exposure to pathogens better off? The answers to both these questions appears to be no.

Antibacterial wipes, soaps, gels, and even toys with antibacterial substances embedded in their plastic are ubiquitous in our society. Still, these products do not rid the skin and gastrointestinal tract of bacteria, and it would be harmful to our health if they did. We need these nonpathogenic bacteria on and within our bodies to keep the pathogenic ones from growing. The urge to keep children perfectly clean is thus probably

misguided. Children will get sick anyway, and the later benefits of immunological memory far outweigh the minor discomforts of most childhood diseases. In fact, getting diseases such as chickenpox or measles later in life is much harder on the adult and are associated with symptoms significantly worse than those seen in the childhood illnesses. Of course, vaccinations help children avoid some illnesses, but there are so many pathogens, we will never be immune to them all.

Could over-cleanliness be the reason that allergies are increasing in more developed countries? Some scientists think so. Allergies are based on an IgE antibody response. Many scientists think the system evolved to help the body rid itself of worm parasites. The hygiene theory is the idea that the immune system is geared to respond to antigens, and if pathogens are not present, it will respond instead to inappropriate antigens such as allergens and self-antigens. This is one explanation for the rising incidence of allergies in developed countries, where the response to nonpathogens like pollen, shrimp, and cat dander cause allergic responses while not serving any protective function.

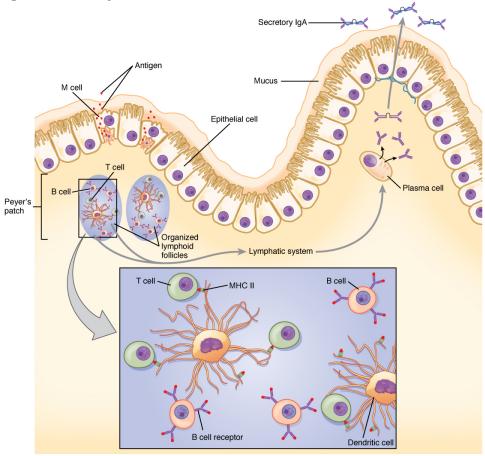
The Mucosal Immune Response

Mucosal tissues are major barriers to the entry of pathogens into the body. The IgA (and sometimes IgM) antibodies in mucus and other secretions can bind to the pathogen, and in the cases of many viruses and bacteria, neutralize them. **Neutralization** is the process of coating a pathogen with antibodies, making it physically impossible for the pathogen to bind to receptors. Neutralization, which occurs in the blood, lymph, and other body fluids and secretions, protects the body constantly. Neutralizing antibodies are the basis for the disease protection offered by vaccines. Vaccinations for diseases that commonly enter the body via mucous membranes, such as influenza, are usually formulated to enhance IgA production.

Immune responses in some mucosal tissues such as the Peyer's patches (see [link]) in the small intestine take up particulate antigens by specialized cells known as microfold or M cells ([link]). These cells allow the body to sample potential pathogens from the intestinal lumen. Dendritic cells then

take the antigen to the regional lymph nodes, where an immune response is mounted.

IgA Immunity



The nasal-associated lymphoid tissue and Peyer's patches of the small intestine generate IgA immunity. Both use M cells to transport antigen inside the body so that immune responses can be mounted.

Defenses against Bacteria and Fungi

The body fights bacterial pathogens with a wide variety of immunological mechanisms, essentially trying to find one that is effective. Bacteria such as *Mycobacterium leprae*, the cause of leprosy, are resistant to lysosomal enzymes and can persist in macrophage organelles or escape into the

cytosol. In such situations, infected macrophages receiving cytokine signals from Th1 cells turn on special metabolic pathways. **Macrophage oxidative metabolism** is hostile to intracellular bacteria, often relying on the production of nitric oxide to kill the bacteria inside the macrophage.

Fungal infections, such as those from *Aspergillus*, *Candida*, and *Pneumocystis*, are largely opportunistic infections that take advantage of suppressed immune responses. Most of the same immune mechanisms effective against bacteria have similar effects on fungi, both of which have characteristic cell wall structures that protect their cells.

Defenses against Parasites

Worm parasites such as helminths are seen as the primary reason why the mucosal immune response, IgE-mediated allergy and asthma, and eosinophils evolved. These parasites were at one time very common in human society. When infecting a human, often via contaminated food, some worms take up residence in the gastrointestinal tract. Eosinophils are attracted to the site by T cell cytokines, which release their granule contents upon their arrival. Mast cell degranulation also occurs, and the fluid leakage caused by the increase in local vascular permeability is thought to have a flushing action on the parasite, expelling its larvae from the body. Furthermore, if IgE labels the parasite, the eosinophils can bind to it by its Fc receptor.

Defenses against Viruses

The primary mechanisms against viruses are NK cells, interferons, and cytotoxic T cells. Antibodies are effective against viruses mostly during protection, where an immune individual can neutralize them based on a previous exposure. Antibodies have no effect on viruses or other intracellular pathogens once they enter the cell, since antibodies are not able to penetrate the plasma membrane of the cell. Many cells respond to viral infections by downregulating their expression of MHC class I molecules. This is to the advantage of the virus, because without class I expression, cytotoxic T cells have no activity. NK cells, however, can recognize virally

infected class I-negative cells and destroy them. Thus, NK and cytotoxic T cells have complementary activities against virally infected cells.

Interferons have activity in slowing viral replication and are used in the treatment of certain viral diseases, such as hepatitis B and C, but their ability to eliminate the virus completely is limited. The cytotoxic T cell response, though, is key, as it eventually overwhelms the virus and kills infected cells before the virus can complete its replicative cycle. Clonal expansion and the ability of cytotoxic T cells to kill more than one target cell make these cells especially effective against viruses. In fact, without cytotoxic T cells, it is likely that humans would all die at some point from a viral infection (if no vaccine were available).

Evasion of the Immune System by Pathogens

It is important to keep in mind that although the immune system has evolved to be able to control many pathogens, pathogens themselves have evolved ways to evade the immune response. An example already mentioned is in *Mycobactrium tuberculosis*, which has evolved a complex cell wall that is resistant to the digestive enzymes of the macrophages that ingest them, and thus persists in the host, causing the chronic disease tuberculosis. This section briefly summarizes other ways in which pathogens can "outwit" immune responses. But keep in mind, although it seems as if pathogens have a will of their own, they do not. All of these evasive "strategies" arose strictly by evolution, driven by selection.

Bacteria sometimes evade immune responses because they exist in multiple strains, such as different groups of *Staphylococcus aureus*. *S. aureus* is commonly found in minor skin infections, such as boils, and some healthy people harbor it in their nose. One small group of strains of this bacterium, however, called methicillin-resistant *Staphylococcus aureus*, has become resistant to multiple antibiotics and is essentially untreatable. Different bacterial strains differ in the antigens on their surfaces. The immune response against one strain (antigen) does not affect the other; thus, the species survives.

Another method of immune evasion is mutation. Because viruses' surface molecules mutate continuously, viruses like influenza change enough each year that the flu vaccine for one year may not protect against the flu common to the next. New vaccine formulations must be derived for each flu season.

Genetic recombination—the combining of gene segments from two different pathogens—is an efficient form of immune evasion. For example, the influenza virus contains gene segments that can recombine when two different viruses infect the same cell. Recombination between human and pig influenza viruses led to the 2010 H1N1 swine flu outbreak.

Pathogens can produce immunosuppressive molecules that impair immune function, and there are several different types. Viruses are especially good at evading the immune response in this way, and many types of viruses have been shown to suppress the host immune response in ways much more subtle than the wholesale destruction caused by HIV.

Chapter Review

Early childhood is a time when the body develops much of its immunological memory that protects it from diseases in adulthood. The components of the immune response that have the maximum effectiveness against a pathogen are often associated with the class of pathogen involved. Bacteria and fungi are especially susceptible to damage by complement proteins, whereas viruses are taken care of by interferons and cytotoxic T cells. Worms are attacked by eosinophils. Pathogens have shown the ability, however, to evade the body's immune responses, some leading to chronic infections or even death. The immune system and pathogens are in a slow, evolutionary race to see who stays on top. Modern medicine, hopefully, will keep the results skewed in humans' favor.

Glossary

macrophage oxidative metabolism metabolism turned on in macrophages by T cell signals that help destroy intracellular bacteria

neutralization

inactivation of a virus by the binding of specific antibody

seroconversion

clearance of pathogen in the serum and the simultaneous rise of serum antibody

OU Human Physiology: Diseases Associated with Depressed or Overactive Immune Responses

By the end of this section, you will be able to:

- Discuss inherited and acquired immunodeficiencies
- Summarize the four types of hypersensitivity
- Explain the mechanism of a Type I immediate hypersensitivity reaction to an allergen
- Give an example of how autoimmune disease breaks tolerance

This section is about how the immune system goes wrong. When it goes haywire, and becomes too weak or too strong, it leads to a state of disease. The factors that maintain immunological homeostasis are complex and incompletely understood.

Immunodeficiencies

As you have seen, the immune system is quite complex. It has many pathways using many cell types and signals. Because it is so complex, there are many ways for it to go wrong. Inherited immunodeficiencies arise from gene mutations that affect specific components of the immune response. There are also acquired immunodeficiencies with potentially devastating effects on the immune system, such as HIV.

Inherited Immunodeficiencies

A list of all inherited immunodeficiencies is well beyond the scope of this book. The list is almost as long as the list of cells, proteins, and signaling molecules of the immune system itself. Some deficiencies, such as those for complement, cause only a higher susceptibility to some Gram-negative bacteria. Others are more severe in their consequences. Certainly, the most serious of the inherited immunodeficiencies is **severe combined immunodeficiency disease (SCID)**. This disease is complex because it is caused by many different genetic defects. What groups them together is the fact that both the B cell and T cell arms of the adaptive immune response are affected.

Children with this disease usually die of opportunistic infections within their first year of life unless they receive a bone marrow transplant. Such a procedure had not yet been perfected for David Vetter, the "boy in the bubble," who was treated for SCID by having to live almost his entire life in a sterile plastic cocoon for the 12 years before his death from infection in 1984. One of the features that make bone marrow transplants work as well as they do is the proliferative capability of hematopoietic stem cells of the bone marrow. Only a small amount of bone marrow from a healthy donor is given intravenously to the recipient. It finds its own way to the bone where it populates it, eventually reconstituting the patient's immune system, which is usually destroyed beforehand by treatment with radiation or chemotherapeutic drugs.

New treatments for SCID using gene therapy, inserting nondefective genes into cells taken from the patient and giving them back, have the advantage of not needing the tissue match required for standard transplants. Although not a standard treatment, this approach holds promise, especially for those in whom standard bone marrow transplantation has failed.

Human Immunodeficiency Virus/AIDS

Although many viruses cause suppression of the immune system, only one wipes it out completely, and that is the previously mentioned HIV. It is worth discussing the biology of this virus, which can lead to the well-known AIDS, so that its full effects on the immune system can be understood. The virus is transmitted through semen, vaginal fluids, and blood, and can be caught by risky sexual behaviors and the sharing of needles by intravenous drug users. There are sometimes, but not always, flu-like symptoms in the first 1 to 2 weeks after infection. This is later followed by seroconversion. The anti-HIV antibodies formed during seroconversion are the basis for most initial HIV screening done in the United States. Because seroconversion takes different lengths of time in different individuals, multiple AIDS tests are given months apart to confirm or eliminate the possibility of infection.

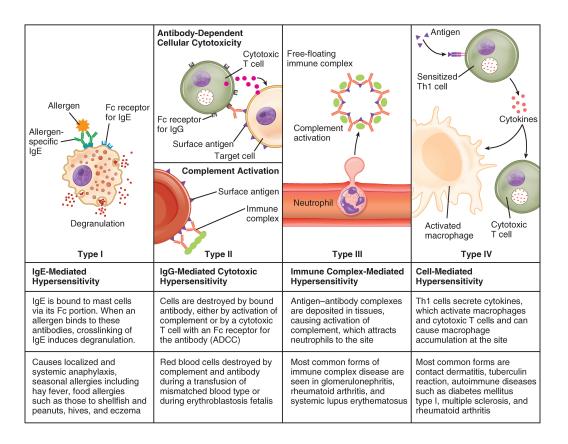
After seroconversion, the amount of virus circulating in the blood drops and stays at a low level for several years. During this time, the levels of CD4⁺ cells, especially helper T cells, decline steadily, until at some point, the immune response is so weak that opportunistic disease and eventually death result. CD4 is the receptor that HIV uses to get inside T cells and reproduce. Given that CD4⁺ helper T cells play an important role in other in T cell immune responses and antibody responses, it should be no surprise that both types of immune responses are eventually seriously compromised.

Treatment for the disease consists of drugs that target virally encoded proteins that are necessary for viral replication but are absent from normal human cells. By targeting the virus itself and sparing the cells, this approach has been successful in significantly prolonging the lives of HIV-positive individuals. On the other hand, an HIV vaccine has been 30 years in development and is still years away. Because the virus mutates rapidly to evade the immune system, scientists have been looking for parts of the virus that do not change and thus would be good targets for a vaccine candidate.

Hypersensitivities

The word "hypersensitivity" simply means sensitive beyond normal levels of activation. Allergies and inflammatory responses to nonpathogenic environmental substances have been observed since the dawn of history. Hypersensitivity is a medical term describing symptoms that are now known to be caused by unrelated mechanisms of immunity. Still, it is useful for this discussion to use the four types of hypersensitivities as a guide to understand these mechanisms ([link]).

Immune Hypersensitivity



Components of the immune system cause four types of hypersensitivity. Notice that types I–III are B cell mediated, whereas type IV hypersensitivity is exclusively a T cell phenomenon.

Immediate (Type I) Hypersensitivity

Antigens that cause allergic responses are often referred to as allergens. The specificity of the **immediate hypersensitivity** response is predicated on the binding of allergen-specific IgE to the mast cell surface. The process of producing allergen-specific IgE is called sensitization, and is a necessary prerequisite for the symptoms of immediate hypersensitivity to occur. Allergies and allergic asthma are mediated by mast cell degranulation that is caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface. The mediators released have various vasoactive effects

already discussed, but the major symptoms of inhaled allergens are the nasal edema and runny nose caused by the increased vascular permeability and increased blood flow of nasal blood vessels. As these mediators are released with mast cell degranulation, **type I hypersensitivity** reactions are usually rapid and occur within just a few minutes, hence the term immediate hypersensitivity.

Most allergens are in themselves nonpathogenic and therefore innocuous. Some individuals develop mild allergies, which are usually treated with antihistamines. Others develop severe allergies that may cause anaphylactic shock, which can potentially be fatal within 20 to 30 minutes if untreated. This drop in blood pressure (shock) with accompanying contractions of bronchial smooth muscle is caused by systemic mast cell degranulation when an allergen is eaten (for example, shellfish and peanuts), injected (by a bee sting or being administered penicillin), or inhaled (asthma). Because epinephrine raises blood pressure and relaxes bronchial smooth muscle, it is routinely used to counteract the effects of anaphylaxis and can be lifesaving. Patients with known severe allergies are encouraged to keep automatic epinephrine injectors with them at all times, especially when away from easy access to hospitals.

Allergists use skin testing to identify allergens in type I hypersensitivity. In skin testing, allergen extracts are injected into the epidermis, and a positive result of a soft, pale swelling at the site surrounded by a red zone (called the wheal and flare response), caused by the release of histamine and the granule mediators, usually occurs within 30 minutes. The soft center is due to fluid leaking from the blood vessels and the redness is caused by the increased blood flow to the area that results from the dilation of local blood vessels at the site.

Type II and Type III Hypersensitivities

Type II hypersensitivity, which involves IgG-mediated lysis of cells by complement proteins, occurs during mismatched blood transfusions and blood compatibility diseases such as erythroblastosis fetalis (see section on transplantation). **Type III hypersensitivity** occurs with diseases such as

systemic lupus erythematosus, where soluble antigens, mostly DNA and other material from the nucleus, and antibodies accumulate in the blood to the point that the antigen and antibody precipitate along blood vessel linings. These immune complexes often lodge in the kidneys, joints, and other organs where they can activate complement proteins and cause inflammation.

Delayed (Type IV) Hypersensitivity

Delayed hypersensitivity, or type IV hypersensitivity, is basically a standard cellular immune response. In delayed hypersensitivity, the first exposure to an antigen is called **sensitization**, such that on re-exposure, a secondary cellular response results, secreting cytokines that recruit macrophages and other phagocytes to the site. These sensitized T cells, of the Th1 class, will also activate cytotoxic T cells. The time it takes for this reaction to occur accounts for the 24- to 72-hour delay in development.

The classical test for delayed hypersensitivity is the tuberculin test for tuberculosis, where bacterial proteins from *M. tuberculosis* are injected into the skin. A couple of days later, a positive test is indicated by a raised red area that is hard to the touch, called an induration, which is a consequence of the cellular infiltrate, an accumulation of activated macrophages. A positive tuberculin test means that the patient has been exposed to the bacteria and exhibits a cellular immune response to it.

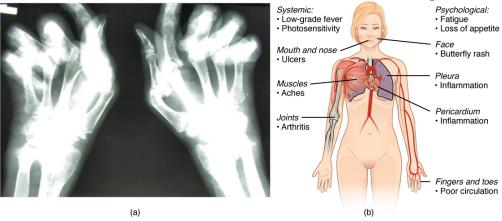
Another type of delayed hypersensitivity is contact sensitivity, where substances such as the metal nickel cause a red and swollen area upon contact with the skin. The individual must have been previously sensitized to the metal. A much more severe case of contact sensitivity is poison ivy, but many of the harshest symptoms of the reaction are associated with the toxicity of its oils and are not T cell mediated.

Autoimmune Responses

The worst cases of the immune system over-reacting are autoimmune diseases. Somehow, tolerance breaks down and the immune systems in

individuals with these diseases begin to attack their own bodies, causing significant damage. The trigger for these diseases is, more often than not, unknown, and the treatments are usually based on resolving the symptoms using immunosuppressive and anti-inflammatory drugs such as steroids. These diseases can be localized and crippling, as in rheumatoid arthritis, or diffuse in the body with multiple symptoms that differ in different individuals, as is the case with systemic lupus erythematosus ([link]).

Autoimmune Disorders: Rheumatoid Arthritis and Lupus



(a) Extensive damage to the right hand of a rheumatoid arthritis sufferer is shown in the x-ray. (b) The diagram shows a variety of possible symptoms of systemic lupus erythematosus.

Environmental triggers seem to play large roles in autoimmune responses. One explanation for the breakdown of tolerance is that, after certain bacterial infections, an immune response to a component of the bacterium cross-reacts with a self-antigen. This mechanism is seen in rheumatic fever, a result of infection with *Streptococcus* bacteria, which causes strep throat. The antibodies to this pathogen's M protein cross-react with an antigenic component of heart myosin, a major contractile protein of the heart that is critical to its normal function. The antibody binds to these molecules and activates complement proteins, causing damage to the heart, especially to the heart valves. On the other hand, some theories propose that having multiple common infectious diseases actually prevents autoimmune responses. The fact that autoimmune diseases are rare in countries that have

a high incidence of infectious diseases supports this idea, another example of the hygiene hypothesis discussed earlier in this chapter.

There are genetic factors in autoimmune diseases as well. Some diseases are associated with the MHC genes that an individual expresses. The reason for this association is likely because if one's MHC molecules are not able to present a certain self-antigen, then that particular autoimmune disease cannot occur. Overall, there are more than 80 different autoimmune diseases, which are a significant health problem in the elderly. [link] lists several of the most common autoimmune diseases, the antigens that are targeted, and the segment of the adaptive immune response that causes the damage.

Autoimmune Diseases		
Disease	Autoantigen	Symptoms
Celiac disease	Tissue transglutaminase Damage to sma	
Diabetes mellitus type I	Low insulin production; Beta cells of pancreas inability to regulate serul glucose	
Graves' disease	Thyroid-stimulating hormone receptor (antibody blocks receptor)	Hyperthyroidism

Autoimmune Diseases		
Disease	Autoantigen	Symptoms
Hashimoto's thyroiditis	Thyroid-stimulating hormone receptor (antibody mimics hormone and stimulates receptor) Hypothyroidism	
Lupus erythematosus	Nuclear DNA and proteins	Damage of many body systems
Myasthenia gravis	Acetylcholine receptor in neuromuscular junctions	Debilitating muscle weakness
Rheumatoid arthritis	Joint capsule antigens	Chronic inflammation of joints

Chapter Review

The immune response can be under-reactive or over-reactive. Suppressed immunity can result from inherited genetic defects or by acquiring viruses. Over-reactive immune responses include the hypersensitivities: B cell- and T cell-mediated immune responses designed to control pathogens, but that lead to symptoms or medical complications. The worst cases of over-reactive immune responses are autoimmune diseases, where an individual's immune system attacks his or her own body because of the breakdown of immunological tolerance. These diseases are more common in the aged, so treating them will be a challenge in the future as the aged population in the world increases.

Glossary

delayed hypersensitivity

(type IV) T cell-mediated immune response against pathogens infiltrating interstitial tissues, causing cellular infiltrate

immediate hypersensitivity

(type I) IgE-mediated mast cell degranulation caused by crosslinking of surface IgE by antigen

sensitization

first exposure to an antigen

severe combined immunodeficiency disease (SCID)

genetic mutation that affects both T cell and B cell arms of the immune response

type I hypersensitivity

immediate response mediated by mast cell degranulation caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface

type II hypersensitivity

cell damage caused by the binding of antibody and the activation of complement, usually against red blood cells

type III hypersensitivity

damage to tissues caused by the deposition of antibody-antigen (immune) complexes followed by the activation of complement

OU Human Physiology: Transplantation and Cancer Immunology By the end of this section, you will be able to:

- Explain why blood typing is important and what happens when mismatched blood is used in a transfusion
- Describe how tissue typing is done during organ transplantation and the role of transplant anti-rejection drugs
- Show how the immune response is able to control some cancers and how this immune response might be enhanced by cancer vaccines

The immune responses to transplanted organs and to cancer cells are both important medical issues. With the use of tissue typing and anti-rejection drugs, transplantation of organs and the control of the anti-transplant immune response have made huge strides in the past 50 years. Today, these procedures are commonplace. **Tissue typing** is the determination of MHC molecules in the tissue to be transplanted to better match the donor to the recipient. The immune response to cancer, on the other hand, has been more difficult to understand and control. Although it is clear that the immune system can recognize some cancers and control them, others seem to be resistant to immune mechanisms.

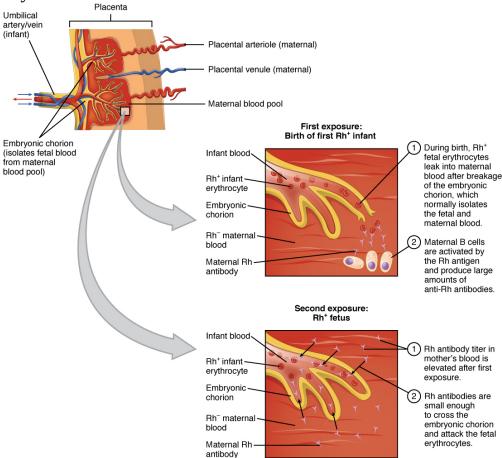
The Rh Factor

Red blood cells can be typed based on their surface antigens. ABO blood type, in which individuals are type A, B, AB, or O according to their genetics, is one example. A separate antigen system seen on red blood cells is the Rh antigen. When someone is "A positive" for example, the positive refers to the presence of the Rh antigen, whereas someone who is "A negative" would lack this molecule.

An interesting consequence of Rh factor expression is seen in **erythroblastosis fetalis**, a hemolytic disease of the newborn ([link]). This disease occurs when mothers negative for Rh antigen have multiple Rh-positive children. During the birth of a first Rh-positive child, the mother makes a primary anti-Rh antibody response to the fetal blood cells that enter the maternal bloodstream. If the mother has a second Rh-positive child, IgG antibodies against Rh-positive blood mounted during this

secondary response cross the placenta and attack the fetal blood, causing anemia. This is a consequence of the fact that the fetus is not genetically identical to the mother, and thus the mother is capable of mounting an immune response against it. This disease is treated with antibodies specific for Rh factor. These are given to the mother during the subsequent births, destroying any fetal blood that might enter her system and preventing the immune response.

Erythroblastosis Fetalis



Erythroblastosis fetalis (hemolytic disease of the newborn) is the result of an immune response in an Rhnegative mother who has multiple children with an Rhpositive father. During the first birth, fetal blood enters the mother's circulatory system, and anti-Rh antibodies are made. During the gestation of the second child, these antibodies cross the placenta and attack the blood of the fetus. The treatment for this disease is to give the mother

anti-Rh antibodies (RhoGAM) during the first pregnancy to destroy Rh-positive fetal red blood cells from entering her system and causing the anti-Rh antibody response in the first place.

Tissue Transplantation

Tissue transplantation is more complicated than blood transfusions because of two characteristics of MHC molecules. These molecules are the major cause of transplant rejection (hence the name "histocompatibility"). MHC polygeny refers to the multiple MHC proteins on cells, and MHC polymorphism refers to the multiple alleles for each individual MHC locus. Thus, there are many alleles in the human population that can be expressed ([link] and [link]). When a donor organ expresses MHC molecules that are different from the recipient, the latter will often mount a cytotoxic T cell response to the organ and reject it. Histologically, if a biopsy of a transplanted organ exhibits massive infiltration of T lymphocytes within the first weeks after transplant, it is a sign that the transplant is likely to fail. The response is a classical, and very specific, primary T cell immune response. As far as medicine is concerned, the immune response in this scenario does the patient no good at all and causes significant harm.

Partial Table of Alleles of the Human MHC (Class I)				
Gene	# of # of possible MHC I protein Gene alleles components			
A	2132	1527		

Partial Table of Alleles of the Human MHC (Class I)		
Gene	# of alleles	# of possible MHC I protein components
В	2798	2110
С	1672	1200
E	11	3
F	22	4
G	50	16

Partial Table of Alleles of the Human MHC (Class II)		
Gene	# of # of possible MHC II protein components	
DRA	7	2
DRB	1297	958
DQA1	49	31
DQB1	179	128
DPA1	36	18
DPB1	158	136

Partial Table of Alleles of the Human MHC (Class II)		
Gene	# of alleles	# of possible MHC II protein components
DMA	7	4
DMB	13	7
DOA	12	3
DOB	13	5

Immunosuppressive drugs such as cyclosporine A have made transplants more successful, but matching the MHC molecules is still key. In humans, there are six MHC molecules that show the most polymorphisms, three class I molecules (A, B, and C) and three class II molecules called DP, DQ, and DR. A successful transplant usually requires a match between at least 3–4 of these molecules, with more matches associated with greater success. Family members, since they share a similar genetic background, are much more likely to share MHC molecules than unrelated individuals do. In fact, due to the extensive polymorphisms in these MHC molecules, unrelated donors are found only through a worldwide database. The system is not foolproof however, as there are not enough individuals in the system to provide the organs necessary to treat all patients needing them.

One disease of transplantation occurs with bone marrow transplants, which are used to treat various diseases, including SCID and leukemia. Because the bone marrow cells being transplanted contain lymphocytes capable of mounting an immune response, and because the recipient's immune response has been destroyed before receiving the transplant, the donor cells may attack the recipient tissues, causing **graft-versus-host disease**. Symptoms of this disease, which usually include a rash and damage to the liver and mucosa, are variable, and attempts have been made to moderate the disease by first removing mature T cells from the donor bone marrow before transplanting it.

Immune Responses Against Cancer

It is clear that with some cancers, for example Kaposi's sarcoma, a healthy immune system does a good job at controlling them ([link]). This disease, which is caused by the human herpesvirus, is almost never observed in individuals with strong immune systems, such as the young and immunocompetent. Other examples of cancers caused by viruses include liver cancer caused by the hepatitis B virus and cervical cancer caused by the human papilloma virus. As these last two viruses have vaccines available for them, getting vaccinated can help prevent these two types of cancer by stimulating the immune response.

Karposi's Sarcoma Lesions



(credit: National Cancer Institute)

On the other hand, as cancer cells are often able to divide and mutate rapidly, they may escape the immune response, just as certain pathogens such as HIV do. There are three stages in the immune response to many cancers: elimination, equilibrium, and escape. Elimination occurs when the immune response first develops toward tumor-specific antigens specific to the cancer and actively kills most cancer cells, followed by a period of controlled equilibrium during which the remaining cancer cells are held in check. Unfortunately, many cancers mutate, so they no longer express any specific antigens for the immune system to respond to, and a subpopulation

of cancer cells escapes the immune response, continuing the disease process.

This fact has led to extensive research in trying to develop ways to enhance the early immune response to completely eliminate the early cancer and thus prevent a later escape. One method that has shown some success is the use of cancer vaccines, which differ from viral and bacterial vaccines in that they are directed against the cells of one's own body. Treated cancer cells are injected into cancer patients to enhance their anti-cancer immune response and thereby prolong survival. The immune system has the capability to detect these cancer cells and proliferate faster than the cancer cells do, overwhelming the cancer in a similar way as they do for viruses. Cancer vaccines have been developed for malignant melanoma, a highly fatal skin cancer, and renal (kidney) cell carcinoma. These vaccines are still in the development stages, but some positive and encouraging results have been obtained clinically.

It is tempting to focus on the complexity of the immune system and the problems it causes as a negative. The upside to immunity, however, is so much greater: The benefit of staying alive far outweighs the negatives caused when the system does sometimes go awry. Working on "autopilot," the immune system helps to maintain your health and kill pathogens. The only time you really miss the immune response is when it is not being effective and illness results, or, as in the extreme case of HIV disease, the immune system is gone completely.

Note:

Everyday Connection

How Stress Affects the Immune Response: The Connections between the Immune, Nervous, and Endocrine Systems of the Body

The immune system cannot exist in isolation. After all, it has to protect the entire body from infection. Therefore, the immune system is required to interact with other organ systems, sometimes in complex ways. Thirty years of research focusing on the connections between the immune system, the central nervous system, and the endocrine system have led to a new science with the unwieldy name of called **psychoneuroimmunology**. The

physical connections between these systems have been known for centuries: All primary and secondary organs are connected to sympathetic nerves. What is more complex, though, is the interaction of neurotransmitters, hormones, cytokines, and other soluble signaling molecules, and the mechanism of "crosstalk" between the systems. For example, white blood cells, including lymphocytes and phagocytes, have receptors for various neurotransmitters released by associated neurons. Additionally, hormones such as cortisol (naturally produced by the adrenal cortex) and prednisone (synthetic) are well known for their abilities to suppress T cell immune mechanisms, hence, their prominent use in medicine as long-term, anti-inflammatory drugs.

One well-established interaction of the immune, nervous, and endocrine systems is the effect of stress on immune health. In the human vertebrate evolutionary past, stress was associated with the fight-or-flight response, largely mediated by the central nervous system and the adrenal medulla. This stress was necessary for survival. The physical action of fighting or running, whichever the animal decides, usually resolves the problem in one way or another. On the other hand, there are no physical actions to resolve most modern day stresses, including short-term stressors like taking examinations and long-term stressors such as being unemployed or losing a spouse. The effect of stress can be felt by nearly every organ system, and the immune system is no exception ([link]).

Effects of Stress on Body Systems		
System	Stress-related illness	
Integumentary system	Acne, skin rashes, irritation	

Effects of Stress on Body Systems		
System	Stress-related illness	
Nervous system	Headaches, depression, anxiety, irritability, loss of appetite, lack of motivation, reduced mental performance	
Muscular and skeletal systems	Muscle and joint pain, neck and shoulder pain	
Circulatory system	Increased heart rate, hypertension, increased probability of heart attacks	
Digestive system	Indigestion, heartburn, stomach pain, nausea, diarrhea, constipation, weight gain or loss	
Immune system	Depressed ability to fight infections	
Male reproductive system	Lowered sperm production, impotence, reduced sexual desire	
Female reproductive system	Irregular menstrual cycle, reduced sexual desire	

At one time, it was assumed that all types of stress reduced all aspects of the immune response, but the last few decades of research have painted a different picture. First, most short-term stress does not impair the immune system in healthy individuals enough to lead to a greater incidence of diseases. However, older individuals and those with suppressed immune responses due to disease or immunosuppressive drugs may respond even to short-term stressors by getting sicker more often. It has been found that

short-term stress diverts the body's resources towards enhancing innate immune responses, which have the ability to act fast and would seem to help the body prepare better for possible infections associated with the trauma that may result from a fight-or-flight exchange. The diverting of resources away from the adaptive immune response, however, causes its own share of problems in fighting disease.

Chronic stress, unlike short-term stress, may inhibit immune responses even in otherwise healthy adults. The suppression of both innate and adaptive immune responses is clearly associated with increases in some diseases, as seen when individuals lose a spouse or have other long-term stresses, such as taking care of a spouse with a fatal disease or dementia. The new science of psychoneuroimmunology, while still in its relative infancy, has great potential to make exciting advances in our understanding of how the nervous, endocrine, and immune systems have evolved together and communicate with each other.

Chapter Review

Blood transfusion and organ transplantation both require an understanding of the immune response to prevent medical complications. Blood needs to be typed so that natural antibodies against mismatched blood will not destroy it, causing more harm than good to the recipient. Transplanted organs must be matched by their MHC molecules and, with the use of immunosuppressive drugs, can be successful even if an exact tissue match cannot be made. Another aspect to the immune response is its ability to control and eradicate cancer. Although this has been shown to occur with some rare cancers and those caused by known viruses, the normal immune response to most cancers is not sufficient to control cancer growth. Thus, cancer vaccines designed to enhance these immune responses show promise for certain types of cancer.

Glossary

erythroblastosis fetalis

disease of Rh factor-positive newborns in Rh-negative mothers with multiple Rh-positive children; resulting from the action of maternal antibodies against fetal blood

graft-versus-host disease

in bone marrow transplants; occurs when the transplanted cells mount an immune response against the recipient

MHC polygeny

multiple MHC genes and their proteins found in body cells

MHC polymorphism

multiple alleles for each individual MHC locus

psychoneuroimmunology

study of the connections between the immune, nervous, and endocrine systems

tissue typing

typing of MHC molecules between a recipient and donor for use in a potential transplantation procedure

OU Human Physiology: Introduction to the Urinary System class="introduction"
Sewage Treatment Plant

(credit: "eutrophication&hypoxia"/flickr.com



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Characterize the roles of each of the parts of the urinary system

- Identify the macroscopic and microscopic structures of the kidney
- Trace the flow of blood through the kidney
- Trace the filtrate from the glomerulus to the urethra
- Outline how blood is filtered in the kidney and the forces that govern filtration
- Describe the mechanism for solute filtration, secretion, and absorption in different parts of the nephron
- Explain how urine osmolarity is hormonally regulated
- Describe the regulation of major ions by the kidney
- Summarize the role of the kidneys in maintaining acid-base balance
- Describe the feedback mechanisms and their role in homeostasis
- Provide specific examples to demonstrate how the urinary system responds to maintain homeostasis in the body
- Explain how the urinary system relates to other body systems in maintaining homeostasis
- Predict factors or situations affecting the urinary system that could disrupt homeostasis
- Predict the types of problems that would occur in the body if the urinary system could not maintain homeostasis

The urinary system has roles you may be well aware of: cleansing the blood and ridding the body of wastes probably come to mind. However, there are additional, equally important functions played by the system. Take for example, regulation of pH, a function shared with the lungs and the buffers in the blood. Additionally, the regulation of blood pressure is a role shared with the heart and blood vessels. What about regulating the concentration of solutes in the blood? Did you know that the kidney is important in determining the concentration of red blood cells? Eighty-five percent of the erythropoietin (EPO) produced to stimulate red blood cell production is produced in the kidneys. The kidneys also perform the final synthesis step of vitamin D production, converting calcidiol to calcitriol, the active form of vitamin D.

If the kidneys fail, these functions are compromised or lost altogether, with devastating effects on homeostasis. The affected individual might

experience weakness, lethargy, shortness of breath, anemia, widespread edema (swelling), metabolic acidosis, rising potassium levels, heart arrhythmias, and more. Each of these functions is vital to your well-being and survival. The urinary system, controlled by the nervous system, also stores urine until a convenient time for disposal and then provides the anatomical structures to transport this waste liquid to the outside of the body. Failure of nervous control or the anatomical structures leading to a loss of control of urination results in a condition called incontinence.

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: "What happens if this does not work?" This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one's life.

Note:



Watch this <u>video</u> from the Howard Hughes Medical Institute for an introduction to the urinary system.

Note:		



Watch this <u>video</u> to learn more about the kidneys.

OU Human Physiology: Physical Characteristics of Urine By the end of this section, you will be able to:

- List the functions of the urinary system
- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Describe the characteristics of a normal urine sample, including normal pH range, osmolarity, and volume

The urinary system's ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors ([link]). Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

Normal Urine Characteristics		
Characteristic	Normal values	
Color	Pale yellow to deep amber	
Odor	Odorless	
Volume	750–2000 mL/24 hour	
pН	4.5–8.0	
Specific gravity	1.003-1.032	
Osmolarity	40–1350 mOsmol/kg	
Urobilinogen	0.2–1.0 mg/100 mL	
White blood cells	0–2 HPF (per high-power field of microscope)	
Leukocyte esterase	None	
Protein	None or trace	
Bilirubin	<0.3 mg/100 mL	
Ketones	None	
Nitrites	None	
Blood	None	
Glucose	None	

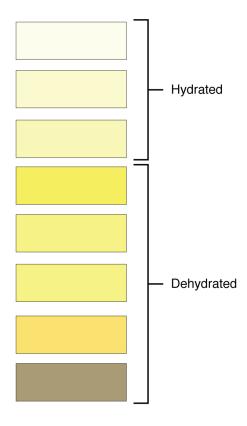
Urinalysis (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the breakdown products of red blood cell destruction ([link]). The "heme" of hemoglobin is converted by the liver into watersoluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is **urochrome**. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark "tea" or "cola" hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.

Note:



Visit this <u>page</u> to learn more how certain foods and medicines affect urine color.

Urine Color



Urine volume varies considerably. The normal range is one to two liters per day ([link]). The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed **oliguria**. The virtual absence of urine production is termed **anuria**. Excessive urine production is **polyuria**, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

Urine Volumes		
Volume condition	Volume	Causes
Normal	1–2 L/day	
Polyuria	>2.5 L/day	Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake
Oliguria	300– 500 mL/day	Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate
Anuria	<50 mL/day	Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH. Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than **specific gravity**. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H₂O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. **Leukocyte esterase** is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to "leak" into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO_3^-) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO_2^-), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.

Chapter Review

The kidney glomerulus filters blood mainly based on particle size to produce a filtrate lacking cells or large proteins. Most of the ions and molecules in the filtrate are needed by the body and must be reabsorbed farther down the nephron tubules, resulting in the formation of urine. Urine characteristics change depending on water intake, exercise, environmental temperature, and nutrient intake. Urinalysis analyzes characteristics of the urine and is used to diagnose diseases. A minimum of 400 to 500 mL urine must be produced daily to rid the body of wastes. Excessive quantities of urine may indicate diabetes insipidus or diabetes mellitus. The pH range of urine is 4.5 to 8.0, and is affected by diet. Osmolarity ranges from 50 to 1200 milliosmoles, and is a reflection of the amount of water being recovered or lost by renal nephrons.

Glossary

anuria

absence of urine produced; production of 50 mL or less per day

leukocyte esterase

enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

oliguria

below normal urine production of 400-500 mL/day

polyuria

urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

specific gravity

weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

urinalysis

analysis of urine to diagnose disease

urochrome

heme-derived pigment that imparts the typical yellow color of urine

OU Human Physiology: Gross Anatomy of Urine Transport By the end of this section, you will be able to:

- Describe the role of the ureters, urinary bladder, and urethra in excretion
- Describe the micturition reflex
- Describe voluntary and involuntary control of micturition

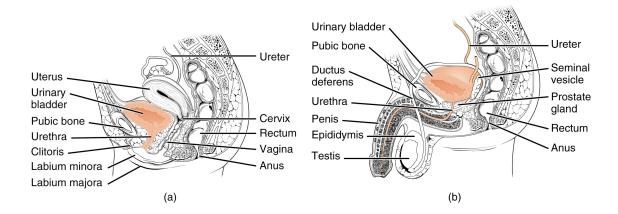
Rather than start with urine formation, this section will start with urine excretion. Urine is a fluid of variable composition that requires specialized structures to remove it from the body safely and efficiently. Blood is filtered, and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for the male, provides reproductive functions.

Urethra

The **urethra** transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical ([link]).

Female and Male Urethras

The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.



Voiding is regulated by both the autonomic nervous system and the somatic nervous system. The autonomic nervous system controls the **internal urinary sphincter** which consists of smooth muscle while the somatic nervous system controls the **external urinary sphincter**.

Female Urethra

The external urethral orifice is embedded in the anterior vaginal wall. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in women. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

Male Urethra

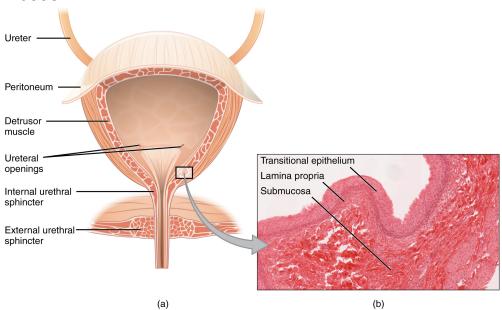
The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (see [link]b). The length of the male urethra varies between men but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from

the seminal vesicles. Bulbourethral glands (Cowper's glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.

Bladder

The urinary bladder collects urine from both ureters ([link]). The bladder is partially **retroperitoneal** (outside the peritoneal cavity) with its peritoneal-covered "dome" projecting into the abdomen when the bladder is distended with urine.

Bladder



(a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Note:



View the University of Michigan WebScope at http://141.214.65.171/Histology/Urinary%20System/212N HISTO 40X.sys/view.apml to explore the tissue sample in greater detail.

The bladder is a highly distensible organ comprised of irregular crisscrossing bands of smooth muscle collectively called the **detrusor muscle**. The interior surface is made of transitional cellular epithelium that is structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it "transitions" (hence the name) to a squamous appearance (see [link]). Volumes in adults can range from nearly zero to 500–600 mL.

The detrusor muscle contracts with significant force in the young. The bladder's strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.

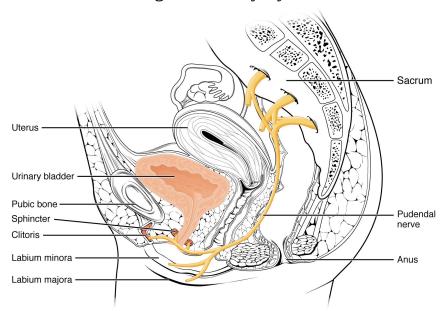
Micturition Reflex

Micturition is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the

internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting **incontinence**, which will occur as bladder volume approaches 300 to 400 mL.

Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex ([link]). The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. Once both sphincters are relaxed, micturition will occur. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves Innervating the Urinary System



Ureters

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The hilum narrows to become the ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates an one-way valve (a **physiological sphincter** rather than an **anatomical sphincter**) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to "vesicoureteral reflux," which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium ([link]) and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall. Ureter



Peristaltic contractions help to move urine through the lumen with contributions from fluid pressure and gravity. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Chapter Review

The urethra is the only urinary structure that differs significantly between males and females. This is due to the dual role of the male urethra in transporting both urine and semen. Urination is controlled by an involuntary internal sphincter of smooth muscle and a voluntary external sphincter of skeletal muscle. The shorter female urethra contributes to the higher incidence of bladder infections in females. The male urethra receives secretions from the prostate gland, Bulbourethral gland, and seminal vesicles as well as sperm. The bladder is largely retroperitoneal and can hold up to 500–600 mL urine. Micturition is the process of voiding the urine and involves both involuntary and voluntary actions. Voluntary

control of micturition requires a mature and intact sacral micturition center. It also requires an intact spinal cord. Loss of control of micturition is called incontinence and results in voiding when the bladder contains about 250 mL urine. The ureters are retroperitoneal and lead from the renal pelvis of the kidney to the base of the bladder. A thick muscular wall consisting of longitudinal and circular smooth muscle helps move urine toward the bladder by way of peristaltic contractions.

Glossary

anatomical sphincter

smooth or skeletal muscle surrounding the lumen of a vessel or hollow organ that can restrict flow when contracted

detrusor muscle

smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

external urinary sphincter

skeletal muscle; must be relaxed consciously to void urine

incontinence

loss of ability to control micturition

internal urinary sphincter

smooth muscle at the juncture of the bladder and urethra; relaxes as the bladder fills to allow urine into the urethra

micturition

also called urination or voiding

physiological sphincter

sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

retroperitoneal

outside the peritoneal cavity; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

urethra

transports urine from the bladder to the outside environment

OU Human Physiology: Gross Anatomy of the Kidney By the end of this section, you will be able to:

- Describe the location of the kidneys
- Identify the major internal divisions and structures of the kidney
- Identify the major blood vessels associated with the kidney and trace the path of blood through the kidney
- Compare and contrast cortical and juxtamedullary nephrons
- Name the structures found in the cortex and medulla
- Describe the physiological characteristics of the cortex and medulla

The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

Note:

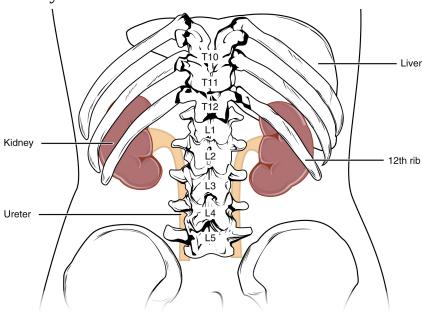


There have never been sufficient kidney donations to provide a kidney to each person needing one. Watch this <u>video</u> to learn about the TED (Technology, Entertainment, Design) Conference held in March 2011. In this video, Dr. Anthony Atala discusses a cutting-edge technique in which a new kidney is "printed." The successful utilization of this technology is still several years in the future, but imagine a time when you can print a replacement organ or tissue on demand.

External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs ([link]). Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the renal fat pad, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.

Kidneys



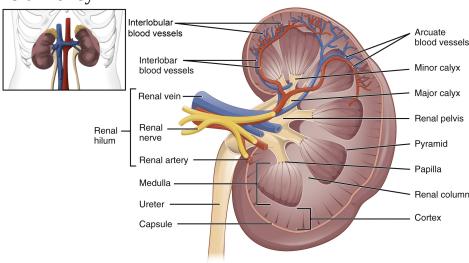
The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the **renal cortex** and an inner region called the **medulla** ([link]). The renal columns are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the **renal pyramids** and **renal papillae**. The papillae are bundles of collecting ducts that transport urine made by nephrons to the **calyces** of the kidney for excretion.





Renal Hilum

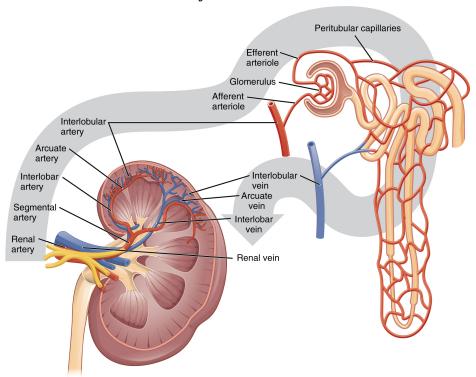
The **renal hilum** is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyxes in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the

descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava.

Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex ([link]). The interlobar arteries, in turn, branch into arcuate arteries, interlobular arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million nephrons in each kidney.

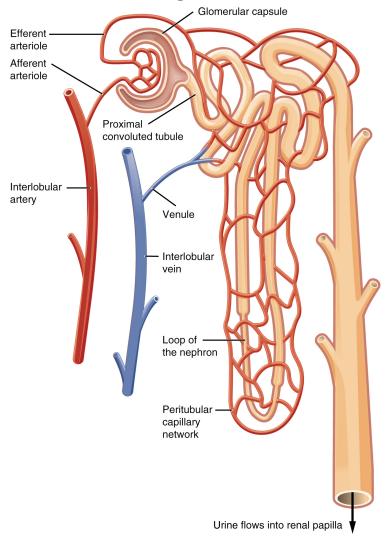
Blood Flow in the Kidney



Nephrons are the "functional units" of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200 µm in diameter, the **glomerulus**. The rest of the nephron consists of a continuous sophisticated tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is **Bowman's capsule**. The glomerulus and Bowman's capsule together form the **renal corpuscle**. As mentioned earlier, these

glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the **efferent arteriole** ([link]). These will next form a capillary network around the more distal portions of the nephron tubule, the **peritubular capillaries** and **vasa recta**, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation.

Blood Flow in the Nephron



The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.

Note:



Visit this <u>link</u> to view an interactive tutorial of the flow of blood through the kidney.

Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the **proximal convoluted tubules (PCTs)** and **distal convoluted tubules** are found here. Some nephrons have a short **loop of Henle** that does not dip beyond the cortex. These nephrons are called **cortical nephrons**. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called **juxtamedullary nephrons**.

Note:



Chapter Review

As noted previously, the structure of the kidney is divided into two principle regions—the peripheral rim of cortex and the central medulla. The two kidneys receive about 25 percent of cardiac output. They are protected in the retroperitoneal space by the renal fat pad and overlying ribs and muscle. Ureters, blood vessels, lymph vessels, and nerves enter and leave at the renal hilum. The renal arteries arise directly from the aorta, and the renal veins drain directly into the inferior vena cava. Kidney function is derived from the actions of about 1.3 million nephrons per kidney; these are the "functional units." A capillary bed, the glomerulus, filters blood and the filtrate is captured by Bowman's capsule. A portal system is formed when the blood flows through a second capillary bed surrounding the proximal and distal convoluted tubules and the loop of Henle. Most water and solutes are recovered by this second capillary bed. This filtrate is processed and finally gathered by collecting ducts that drain into the minor calyces, which merge to form major calvces; the filtrate then proceeds to the renal pelvis and finally the ureters.

Glossary

Bowman's capsule

cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

calyces

cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

cortical nephrons

nephrons with loops of Henle that do not extend into the renal medulla

distal convoluted tubules

portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

efferent arteriole

arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

glomerulus

tuft of capillaries surrounded by Bowman's capsule; filters the blood based on size

juxtamedullary nephrons

nephrons adjacent to the border of the cortex and medulla with loops of Henle that extend into the renal medulla

loop of Henle

descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

medulla

inner region of kidney containing the renal pyramids

nephrons

functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

peritubular capillaries

second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

proximal convoluted tubules (PCTs)

tortuous tubules receiving filtrate from Bowman's capsule; most active part of the nephron in reabsorption and secretion

renal corpuscle

consists of the glomerulus and Bowman's capsule

renal cortex

outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

renal fat pad

adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

renal hilum

recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

renal papillae

medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

renal pyramids

six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

vasa recta

branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system OU Human Physiology: Microscopic Anatomy of the Kidney By the end of this section, you will be able to:

- Describe the function of the nephron including the three principle processes occurring in the nephron
- Trace the filtrate from the glomerulus to the urethra
- Describe the structure and function of the filtration membrane
- Identify the major structures and subdivisions of the renal corpuscle, renal tubules, and renal capillaries
- Discuss the function of the peritubular capillaries and vasa recta
- Identify the location of the juxtaglomerular apparatus and describe the cells that line it

The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

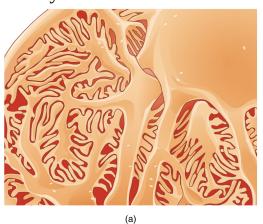
Nephrons: The Functional Unit

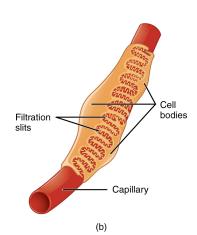
Nephrons take a simple filtrate of the blood and modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term **forming urine** will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of **renin**), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman's (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman's capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells (podocytes) extending finger-like arms (**pedicels**) to cover the glomerular capillaries ([link]). These projections interdigitate to form **filtration slits**, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte "fingers," the only thing separating the capillary lumen and the lumen of Bowman's capsule is their shared basement membrane ([link]). These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule though pores that are only 70 nm in diameter.

Podocytes

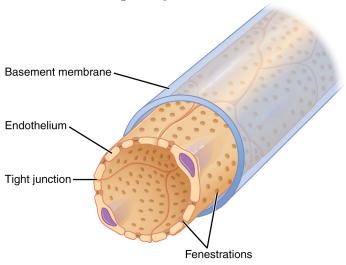




Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels.

Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.

Fenestrated Capillary



Fenestrations allow many substances to diffuse from the blood based primarily on size.

The **fenestrations** prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also **mesangial** cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between

capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Note:

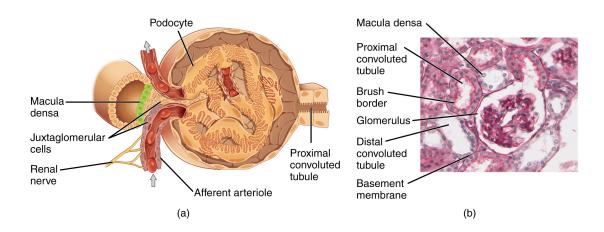


Watch this <u>video</u> to learn more about glomerular filtration in the nephron.

Lying just outside Bowman's capsule and the glomerulus is the **juxtaglomerular apparatus (JGA)** ([link]). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the **macula densa**. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na⁺ in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in response to changes in flow rate and Na⁺ concentration are adenosine triphosphate (ATP) and adenosine.

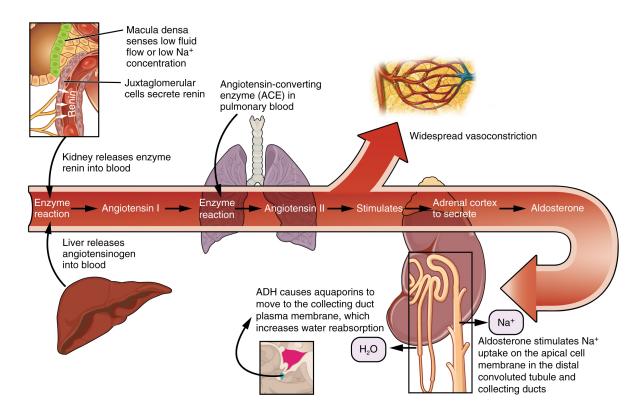
Juxtaglomerular Apparatus and Glomerulus

(a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM × 1540. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



A second cell type in this apparatus is the **juxtaglomerular cell**. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax, increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when osmolarity goes up, filtration and urine formation decrease and water is retained. When osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole ([link]). Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from angiotensinogen to produce **angiotensin I**. Angiotensin I is not biologically active until converted to angiotensin II by **angiotensin-converting enzyme (ACE)** from the lungs. **Angiotensin II** is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates Na⁺ reabsorption by the kidney, which also results in water retention and increased blood pressure.

Conversion of Angiotensin I to Angiotensin II



The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.

Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a brush border. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na⁺, Cl⁻, glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consists of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

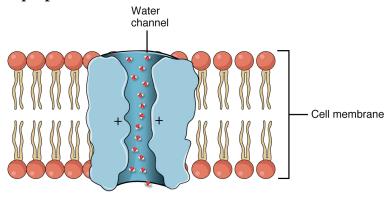
The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT. The DCT contains receptors for ADH which when stimulated will result in the insertion of aquaporins into the membrane.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert **aquaporin** channel proteins into their membranes, which as their name suggests, allow water to pass from

the duct lumen through the cells and into the interstitial spaces to be recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH, these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane ([link]).

Aquaporin Water Channel



Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.

Chapter Review

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle extending into the medulla. About 15 percent of nephrons are juxtamedullary. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman's capsule and directed to the PCT. A filtration membrane is formed by the fused basement membranes of the podocytes and the capillary endothelial

cells that they embrace. Contractile mesangial cells further perform a role in regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

Glossary

angiotensin-converting enzyme (ACE)

enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

angiotensin I

protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

angiotensin II

protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

angiotensinogen

inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to be activated

aquaporin

protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

fenestrations

small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell without mixing with cell contents

filtration slits

formed by pedicels of podocytes; substances filter between the pedicels based on size

forming urine

filtrate undergoing modifications through secretion and reabsorption before true urine is produced

juxtaglomerular apparatus (JGA)

located at the juncture of the DCT and the afferent and efferent arterioles of the glomerulus; plays a role in the regulation of renal blood flow and GFR

juxtaglomerular cell

modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure

macula densa

cells found in the part of the DCT forming the JGA; sense Na⁺ concentration in the forming urine

mesangial

contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

pedicels

finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

podocytes

cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

renin

enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I

OU Human Physiology: Physiology of Urine Formation By the end of this section, you will be able to:

- Describe the hydrostatic and glomerular osmotic forces that favor and oppose filtration
- Infer how changes in hydrostatic and glomerular osmotic forces will alter net filtration pressure (NFP)
- Describe glomerular filtration rate (GFR) and state the average value for GFR
- Predict specific factors that will increase or decrease GFR
- State the percent of filtrate that is normally reabsorbed and explain why the process of reabsorption is so important
- List common symptoms of kidney failure

Having reviewed the anatomy and microanatomy of the urinary system, now is the time to focus on the physiology. You will discover that different parts of the nephron utilize specific processes to produce urine: filtration, reabsorption, and secretion. You will learn how each of these processes works and where they occur along the nephron and collecting ducts. The physiologic goal is to modify the composition of the plasma and, in doing so, produce the waste product urine.

Failure of the renal anatomy and/or physiology can lead suddenly or gradually to renal failure. In this event, a number of symptoms, signs, or laboratory findings point to the diagnosis ([link]).

Symptoms of Kidney Failure
Weakness
Lethargy

Symptoms of Kidney Failure
Shortness of breath
Widespread edema
Anemia
Metabolic acidosis
Metabolic alkalosis
Heart arrhythmias
Uremia (high urea level in the blood)
Loss of appetite
Fatigue
Excessive urination
Oliguria (too little urine output)

Glomerular Filtration Rate (GFR)

The volume of filtrate formed by both kidneys per minute is termed the **glomerular filtration rate (GFR)**. The heart pumps about 5 L blood per min under resting conditions. Approximately 20 percent or one liter enters the kidneys to be filtered. On average, this liter results in the production of about 125 mL/min filtrate produced in men (range of 90 to 140 mL/min) and 105 mL/min filtrate produced in women (range of 80 to 125 mL/min). This amount equates to a volume of about 180 L/day in men and 150 L/day in women. Ninety-nine percent of this filtrate is returned to the circulation by reabsorption so that only about 1–2 liters of urine are produced per day ([link]).

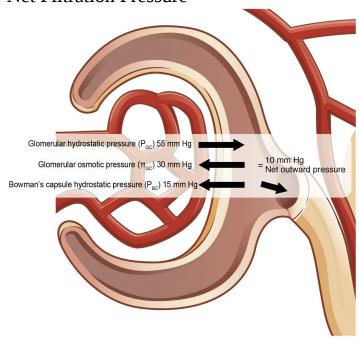
Calculating Urine Formation per Day		
	Flow per minute (mL)	Calculation
Renal blood flow	1050	Cardiac output is about 5000 mL/minute, of which 21 percent flows through the kidney. 5000*0.21 = 1050 mL blood/min
Renal plasma flow	578	Renal plasma flow equals the blood flow per minute times the hematocrit. If a person has a hematocrit of 45, then the renal plasma flow is 55 percent. 1050*0.55 = 578 mL plasma/min
Glomerular filtration rate	110	The GFR is the amount of plasma entering Bowman's capsule per minute. It is the renal plasma flow times the fraction that enters the renal capsule (19 percent). 578*0.19 = 110 mL filtrate/min

Calculating Urine Formation per Day		
	Flow per minute (mL)	Calculation
Urine	1296 ml/day	The filtrate not recovered by the kidney is the urine that will be eliminated. It is the GFR times the fraction of the filtrate that is not reabsorbed (0.8 percent). 110*.08 = 0.9 mL urine /min Multiply urine/min times 60 minutes times 24 hours to get daily urine production. 0.9*60*24 = 1296 mL/day urine

GFR is influenced by the hydrostatic pressure and colloid osmotic pressure on either side of the capillary membrane of the glomerulus. Recall that filtration occurs as pressure forces fluid and solutes through a semipermeable barrier with the solute movement constrained by particle size. Hydrostatic pressure is the pressure produced by a fluid against a surface. If you have a fluid on both sides of a barrier, both fluids exert a pressure in opposing directions. Net fluid movement will be in the direction of the lower pressure. Osmosis is the movement of solvent (water) across a membrane that is impermeable to a solute in the solution. This creates a pressure, osmotic pressure, which will exist until the solute concentration is the same on both sides of a semipermeable membrane. As long as the concentration differs, water will move. Glomerular filtration occurs when glomerular hydrostatic pressure (P_{GC}) exceeds the luminal hydrostatic pressure of Bowman's capsule (P_{BC}). There is also an opposing force, the glomerular osmotic pressure (π_{GC}), which is typically higher in the glomerular capillary.

To understand why this is so, look more closely at the microenvironment on either side of the filtration membrane. You will find osmotic pressure exerted by the solutes inside the lumen of the capillary as well as inside of Bowman's capsule. Since the filtration membrane limits the size of particles crossing the membrane, the osmotic pressure inside the glomerular capillary (π_{GC}) is higher than the osmotic pressure in Bowman's capsule (π_{BC}) . Recall that cells and the medium-to-large proteins cannot pass between the podocyte processes or through the fenestrations of the capillary endothelial cells. This means that red and white blood cells, platelets, albumins, and other proteins too large to pass through the filter remain in the capillary, creating an average glomerular osmotic pressure of 30 mm Hg within the capillary. The absence of proteins in Bowman's space (the lumen within Bowman's capsule) results in a Bowman's capsule osmotic pressure (π_{BC}) near zero. Thus, the only pressure moving fluid across the capillary wall into the lumen of Bowman's space is glomerular hydrostatic pressure (P_{GC}. Hydrostatic (fluid) pressure is sufficient to push water through the membrane despite the osmotic pressure working against it. The sum of all of the influences, both osmotic and hydrostatic, results in a **net filtration pressure (NFP)** of about 10 mm Hg ([link]). Please note: NFP may also be referred to as glomerular filtration pressure (GFP).

Net Filtration Pressure



The NFP is the sum of osmotic and

hydrostatic pressures.

A proper concentration of solutes in the blood is important in maintaining osmotic pressure both in the glomerulus and systemically. There are disorders in which too much protein passes through the filtration slits into the kidney filtrate. This excess protein in the filtrate leads to a deficiency of circulating plasma proteins. In turn, the presence of protein in the urine increases its osmolarity; this holds more water in the filtrate and results in an increase in urine volume. Because there is less circulating protein, principally albumin, the osmotic pressure of the blood falls. Less osmotic pressure pulling water into the capillaries tips the balance towards hydrostatic pressure, which tends to push it out of the capillaries. The net effect is that water is lost from the circulation to interstitial tissues and cells. This "plumps up" the tissues and cells, a condition termed **systemic edema**.

Net Filtration Pressure (NFP)

NFP determines filtration rates through the kidney. It is determined as follows:

NFP = [Glomerular capillary hydrostatic pressure (P_{GC}) + Bowman's capsule osmotic pressure (π_{BC})] – [Bowman's capsule hydrostatic pressure (π_{BC}) + Glomerular capillary osmotic pressure (π_{GC}))] = 10 mm Hg

That is:

NFP =
$$(P_{GC} + \pi_{BC}) - (P_{BC} + \pi_{GC}) = 10 \text{ mm Hg}$$

Or:

$$NFP = (55-0) - (15 + 30) = 10 \text{ mm Hg}$$

As you can see, there is a low net pressure across the filtration membrane. Intuitively, you should realize that minor changes in osmolarity of the blood or changes in capillary blood pressure result in major changes in the amount

of filtrate formed at any given point in time. The kidney is able to cope with a wide range of blood pressures. In large part, this is due to the autoregulatory nature of smooth muscle. When you stretch it, it contracts. Thus, when blood pressure goes up, smooth muscle in the afferent capillaries contracts to limit any increase in blood flow and filtration rate. When blood pressure drops, the same capillaries relax to maintain blood flow and filtration rate. The net result is a relatively steady flow of blood into the glomerulus and a relatively steady filtration rate in spite of significant systemic blood pressure changes. Mean arterial blood pressure is calculated by adding 1/3 of the difference between the systolic and diastolic pressures to the diastolic pressure. Therefore, if the blood pressure is 110/80, the difference between systolic and diastolic pressure is 30. One third of this is 10, and when you add this to the diastolic pressure of 80, you arrive at a calculated mean arterial pressure of 90 mm Hg. Therefore, if you use mean arterial pressure for the GBHP in the formula for calculating NFP, you can determine that as long as mean arterial pressure is above approximately 60 mm Hg, the pressure will be adequate to maintain glomerular filtration. Blood pressures below this level will impair renal function and cause systemic disorders that are severe enough to threaten survival. This condition is called shock.

Determination of the GFR is one of the tools used to assess the kidney's excretory function. This is more than just an academic exercise. Since many drugs are excreted in the urine, a decline in renal function can lead to toxic accumulations. Additionally, administration of appropriate drug dosages for those drugs primarily excreted by the kidney requires an accurate assessment of GFR. GFR can be estimated closely by intravenous administration of inulin. Inulin is a plant polysaccharide that is neither reabsorbed nor secreted by the kidney. Its appearance in the urine is directly proportional to the rate at which it is filtered by the renal corpuscle. However, since measuring inulin clearance is cumbersome in the clinical setting, most often, the GFR is estimated by measuring naturally occurring creatinine, a protein-derived molecule produced by muscle metabolism that is not reabsorbed and only slightly secreted by the nephron.

Chapter Review

The entire volume of the blood is filtered through the kidneys about 300 times per day, and 99 percent of the water filtered is recovered. The GFR is influenced by hydrostatic pressure and colloid osmotic pressure. Under normal circumstances, hydrostatic pressure is significantly greater and filtration occurs. The hydrostatic pressure of the glomerulus depends on systemic blood pressure, autoregulatory mechanisms, sympathetic nervous activity, and paracrine hormones. The kidney can function normally under a wide range of blood pressures due to the autoregulatory nature of smooth muscle.

Glossary

glomerular filtration rate (GFR) rate of renal filtration

net filtration pressure (NFP)

pressure of fluid across the glomerulus; calculated by taking the hydrostatic pressure of the capillary and subtracting the colloid osmotic pressure of the blood and the hydrostatic pressure of Bowman's capsule

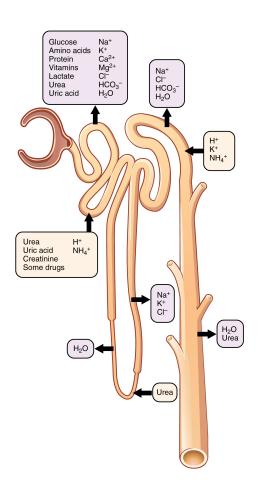
systemic edema

increased fluid retention in the interstitial spaces and cells of the body; can be seen as swelling over large areas of the body, particularly the lower extremities

OU Human Physiology: Tubular Reabsorption By the end of this section, you will be able to:

- List specific transport mechanisms occurring in different parts of the nephron, including active transport, osmosis, facilitated diffusion, and passive electrochemical gradients
- List the different membrane proteins of the nephron, including channels, transporters, and ATPase pumps
- Compare and contrast passive and active tubular reabsorption
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation
- Describe how and where water, organic compounds, and ions are reabsorbed in the nephron
- Explain the role of the loop of Henle, the vasa recta, and the countercurrent multiplication mechanisms in the concentration of urine
- List the locations in the nephron where tubular secretion occurs

With up to 180 liters per day passing through the nephrons of the kidney, it is quite obvious that most of that fluid and its contents must be reabsorbed. That recovery occurs in the PCT, loop of Henle, DCT, and the collecting ducts ([link] and [link]). Various portions of the nephron differ in their capacity to reabsorb water and specific solutes. While much of the reabsorption and secretion occur passively based on concentration gradients, the amount of water that is reabsorbed or lost is tightly regulated. This control is exerted directly by ADH and aldosterone, and indirectly by renin. Most water is recovered in the PCT, loop of Henle, and DCT. About 10 percent (about 18 L) reaches the collecting ducts. The collecting ducts, under the influence of ADH, can recover almost all of the water passing through them, in cases of dehydration, or almost none of the water, in cases of over-hydration. Locations of Secretion and Reabsorption in the Nephron



Substances Secreted or Reabsorbed in the Nephron and Their Locations				
Substance	PCT	Loop of Henle	DCT	Collecting ducts
Glucose	Almost 100 percent reabsorbed; secondary active transport with Na ⁺			

Substances Secreted or Reabsorbed in the Nephron and Their Locations				ations
Substance	PCT	Loop of Henle	DCT	Collecting ducts
Oligopeptides, proteins, amino acids	Almost 100 percent reabsorbed; symport with Na ⁺			
Vitamins	Reabsorbed			
Lactate	Reabsorbed			
Creatinine	Secreted			
Urea	50 percent reabsorbed by diffusion; also secreted	Secretion, diffusion in descending limb		Reabsorption in medullary collecting ducts; diffusion
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with Na ⁺ , diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport

Substances Sec	reted or Reabsorb	ed in the Nephro	on and Their Loca	ations
Substance	PCT	Loop of Henle	DCT	Collecting ducts
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis
Bicarbonate	80–90 percent symport reabsorption with Na ⁺	Reabsorbed, symport with Na ⁺ and antiport with Cl ⁻ ; in ascending limb		Reabsorbed antiport with Cl ⁻
H^{+}	Secreted; diffusion		Secreted; active	Secreted; active
NH ₄ ⁺	Secreted; diffusion		Secreted; diffusion	Secreted; diffusion
HCO ₃ ⁻	Reabsorbed; diffusion	Reabsorbed; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; antiport with Na ⁺
Some drugs	Secreted		Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active

Substances Secreted or Reabsorbed in the Nephron and Their Locations				
Substance	PCT	Loop of Henle	DCT	Collecting ducts
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion		Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	Reabsorbed	
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion		Reabsorbed; diffusion	

Mechanisms of Recovery

Mechanisms by which substances move across membranes for reabsorption or secretion include active transport, diffusion, facilitated diffusion, secondary active transport, and osmosis. These were discussed in an earlier chapter, and you may wish to review them.

Active transport utilizes energy, usually the energy found in a phosphate bond of ATP, to move a substance across a membrane from a low to a high concentration. It is very specific and must have an appropriately shaped receptor for the substance to be transported. An example would be the active transport of Na^+ out of a cell and K^+ into a cell by the $\mathrm{Na}^+/\mathrm{K}^+$ pump. Both ions are moved in opposite directions from a lower to a higher concentration.

Simple diffusion moves a substance from a higher to a lower concentration down its concentration gradient. It requires no energy and only needs to be soluble.

Facilitated diffusion is similar to diffusion in that it moves a substance down its concentration gradient. The difference is that it requires specific membrane receptors or channel proteins for movement. The movement of glucose and, in certain situations, Na⁺ ions, is an example of facilitated diffusion. In some cases of facilitated diffusion, two

different substances share the same channel protein port; these mechanisms are described by the terms symport and antiport.

Symport mechanisms move two or more substances in the same direction at the same time, whereas antiport mechanisms move two or more substances in opposite directions across the cell membrane. Both mechanisms may utilize concentration gradients maintained by ATP pumps. This is a mechanism described by the term "secondary active transport." For example, a Na⁺ ATPase pump on the basilar membrane of a cell may constantly pump Na⁺ out of a cell, maintaining a strong electrochemical gradient. On the opposite (apical) surface, a Na⁺/glucose symport protein channel assists both Na⁺ and glucose into the cell as Na⁺ moves down the concentration gradient created by the basilar Na⁺ ATPase pumps. The glucose molecule then diffuses across the basal membrane by facilitated diffusion into the interstitial space and from there into peritubular capillaries.

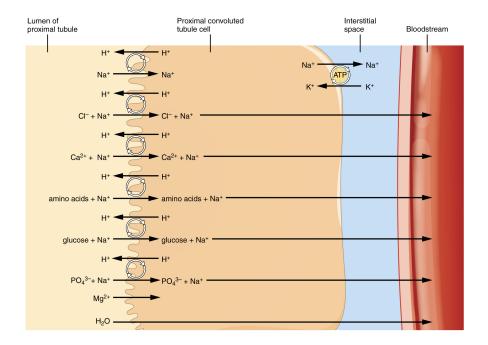
Most of the Ca^{++} , Na^{+} , glucose, and amino acids must be reabsorbed by the nephron to maintain homeostatic plasma concentrations. Other substances, such as urea, K^{+} , ammonia (NH_{3}), creatinine, and some drugs are secreted into the filtrate as waste products. Acid—base balance is maintained through actions of the lungs and kidneys: The lungs rid the body of H^{+} , whereas the kidneys secrete or reabsorb H^{+} and HCO_{3}^{-} ([link]). In the case of urea, about 50 percent is passively reabsorbed by the PCT. More is recovered by in the collecting ducts as needed. ADH induces the insertion of urea transporters and aquaporin channel proteins.

Substances Filtered and Reabsorbed by the Kidney per 24 Hours			
Substance	Amount filtered (grams)	Amount reabsorbed (grams)	Amount in urine (grams)
Water	180 L	179 L	1 L
Proteins	10–20	10–20	0
Chlorine	630	625	5
Sodium	540	537	3
Bicarbonate	300	299.7	0.3
Glucose	180	180	0

Substances Filtered and Reabsorbed by the Kidney per 24 Hours			
Substance	Amount filtered (grams)	Amount reabsorbed (grams)	Amount in urine (grams)
Urea	53	28	25
Potassium	28	24	4
Uric acid	8.5	7.7	0.8
Creatinine	1.4	0	1.4

Reabsorption and Secretion in the PCT

The renal corpuscle filters the blood to create a filtrate that differs from blood mainly in the absence of cells and large proteins. From this point to the ends of the collecting ducts, the filtrate or forming urine is undergoing modification through secretion and reabsorption before true urine is produced. The first point at which the forming urine is modified is in the PCT. Here, some substances are reabsorbed, whereas others are secreted. Note the use of the term "reabsorbed." All of these substances were "absorbed" in the digestive tract— 99 percent of the water and most of the solutes filtered by the nephron must be reabsorbed. Water and substances that are reabsorbed are returned to the circulation by the peritubular and vasa recta capillaries. It is important to understand the difference between the glomerulus and the peritubular and vasa recta capillaries. The glomerulus has a relatively high pressure inside its capillaries and can sustain this by dilating the afferent arteriole while constricting the efferent arteriole. This assures adequate filtration pressure even as the systemic blood pressure varies. Movement of water into the peritubular capillaries and vasa recta will be influenced primarily by osmolarity and concentration gradients. Sodium is actively pumped out of the PCT into the interstitial spaces between cells and diffuses down its concentration gradient into the peritubular capillary. As it does so, water will follow passively to maintain an isotonic fluid environment inside the capillary. This is called obligatory water reabsorption, because water is "obliged" to follow the Na⁺ ([link]). Substances Reabsorbed and Secreted by the PCT



More substances move across the membranes of the PCT than any other portion of the nephron. Many of these substances (amino acids and glucose) use symport mechanisms for transport along with Na⁺. Antiport, active transport, diffusion, and facilitated diffusion are additional mechanisms by which substances are moved from one side of a membrane to the other. Recall that cells have two surfaces: apical and basal. The apical surface is the one facing the lumen or open space of a cavity or tube, in this case, the inside of the PCT. The basal surface of the cell faces the connective tissue base to which the cell attaches (basement membrane) or the cell membrane closer to the basement membrane if there is a stratified layer of cells. In the PCT, there is a single layer of simple cuboidal endothelial cells against the basement membrane. The numbers and particular types of pumps and channels vary between the apical and basilar surfaces ([link]). A few of the substances that are transported with Na⁺ (symport mechanism) on the apical membrane include Cl⁻, Ca⁺⁺, amino acids, glucose, and PO_4^{3-} . Sodium is actively exchanged for K^+ using ATP on the basal membrane. Most of the substances transported by a symport mechanism on the apical membrane are transported by facilitated diffusion on the basal membrane. At least three ions, K⁺, Ca⁺⁺, and Mg⁺⁺, diffuse laterally between adjacent cell membranes (transcellular).

Reabsorption of Major Solutes by the PCT	
Basal membrane	Apical membrane

Reabsorption of Major Solutes by the PCT		
Basal membrane	Apical membrane	
Active transport	Symport with Na ⁺	
Na ⁺ (exchange for K ⁺)	K^{+}	
Facilitated diffusion	Cl ⁻	
K ⁺	Ca ⁺⁺	
Cl-	Mg ⁺⁺	
Ca ⁺⁺	HCO ₃ ⁻	
HCO ₃ ⁻	PO_4^{3-}	
PO_4^{3-}	Amino acids	
Amino acids	Glucose	
Glucose	Fructose	
Fructose	Galactose	
Galactose	Lactate	
Lactate	Succinate	
Succinate	Citrate	
Citrate	Diffusion between nephron cells	
	K ⁺	
	Ca ⁺⁺	
	Mg ⁺⁺	

About 67 percent of the water, Na^+ , and K^+ entering the nephron is reabsorbed in the PCT and returned to the circulation. Almost 100 percent of glucose, amino acids, and other organic substances such as vitamins are normally recovered here. Some glucose may appear

in the urine if circulating glucose levels are high enough that all the glucose transporters in the PCT are saturated, so that their capacity to move glucose is exceeded (transport maximum, or T_m). In men, the maximum amount of glucose that can be recovered is about 375 mg/min, whereas in women, it is about 300 mg/min. This recovery rate translates to an arterial concentration of about 200 mg/dL. Though an exceptionally high sugar intake might cause sugar to appear briefly in the urine, the appearance of **glycosuria** usually points to type I or II diabetes mellitus. The transport of glucose from the lumen of the PCT to the interstitial space is similar to the way it is absorbed by the small intestine. Both glucose and Na⁺ bind simultaneously to the same symport proteins on the apical surface of the cell to be transported in the same direction, toward the interstitial space. Sodium moves down its electrochemical and concentration gradient into the cell and takes glucose with it. Na⁺ is then actively pumped out of the cell at the basal surface of the cell into the interstitial space. Glucose leaves the cell to enter the interstitial space by facilitated diffusion. The energy to move glucose comes from the Na⁺/K⁺ ATPase that pumps Na⁺ out of the cell on the basal surface. Fifty percent of Cl⁻ and variable quantities of Ca⁺⁺, Mg⁺⁺, and HPO_4^{2-} are also recovered in the PCT.

Recovery of bicarbonate (HCO₃⁻) is vital to the maintenance of acid–base balance, since it is a very powerful and fast-acting buffer. An important enzyme is used to catalyze this mechanism: carbonic anhydrase (CA). This same enzyme and reaction is used in red blood cells in the transportation of CO₂, in the stomach to produce hydrochloric acid, and in the pancreas to produce HCO₃⁻ to buffer acidic chyme from the stomach. In the kidney, most of the CA is located within the cell, but a small amount is bound to the brush border of the membrane on the apical surface of the cell. In the lumen of the PCT, HCO₃⁻ combines with hydrogen ions to form carbonic acid (H₂CO₃). This is enzymatically catalyzed into CO₂ and water, which diffuse across the apical membrane into the cell. Water can move osmotically across the lipid bilayer membrane due to the presence of aquaporin water channels. Inside the cell, the reverse reaction occurs to produce bicarbonate ions (HCO₃⁻). These bicarbonate ions are cotransported with Na⁺ across the basal membrane to the interstitial space around the PCT ([link]). At the same time this is occurring, a Na⁺/H⁺ antiporter excretes H⁺ into the lumen, while it recovers Na⁺. Note how the hydrogen ion is recycled so that bicarbonate can be recovered. Also, note that a Na⁺ gradient is created by the Na⁺/K⁺ pump.

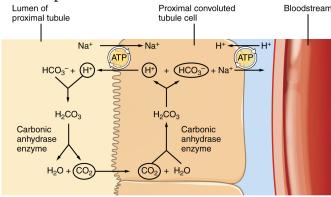
Equation:

$$\mathrm{HCO_{3-}} + \mathrm{H^{+}} \leftrightarrow \mathrm{H_{2}CO_{3}} \leftrightarrow \mathrm{CO_{2}} + \mathrm{H_{2}O}$$

The significant recovery of solutes from the PCT lumen to the interstitial space creates an osmotic gradient that promotes water recovery. As noted before, water moves through channels created by the aquaporin proteins. These proteins are found in all cells in varying amounts and help regulate water movement across membranes and through cells by creating a passageway across the hydrophobic lipid bilayer membrane. Changing the number of aquaporin proteins in membranes of the collecting ducts also helps to regulate the osmolarity of the blood. The movement of many positively charged ions also creates an

electrochemical gradient. This charge promotes the movement of negative ions toward the interstitial spaces and the movement of positive ions toward the lumen.

Reabsorption of Bicarbonate from the PCT



Reabsorption and Secretion in the Loop of Henle

The loop of Henle consists of two sections: thick and thin descending and thin and thick ascending sections. The loops of cortical nephrons do not extend into the renal medulla very far, if at all. Juxtamedullary nephrons have loops that extend variable distances, some very deep into the medulla. The descending and ascending portions of the loop are highly specialized to enable recovery of much of the Na⁺ and water that were filtered by the glomerulus. As the forming urine moves through the loop, the osmolarity will change from isosmotic with blood (about 278–300 mOsmol/kg) to both a very hypertonic solution of about 1200 mOsmol/kg and a very hypotonic solution of about 100 mOsmol/kg. These changes are accomplished by osmosis in the descending limb and active transport in the ascending limb. Solutes and water recovered from these loops are returned to the circulation by way of the vasa recta.

Descending Loop

The majority of the descending loop is comprised of simple squamous epithelial cells; to simplify the function of the loop, this discussion focuses on these cells. These membranes have permanent aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding interstitium as osmolarity increases from about 300 mOsmol/kg to about 1200 mOsmol/kg. This increase results in reabsorption of up to 15 percent of the water entering the nephron. Modest amounts of urea, Na⁺, and other ions are also recovered here.

Most of the solutes that were filtered in the glomerulus have now been recovered along with a majority of water, about 82 percent. As the forming urine enters the ascending loop, major adjustments will be made to the concentration of solutes to create what you perceive as urine.

Ascending Loop

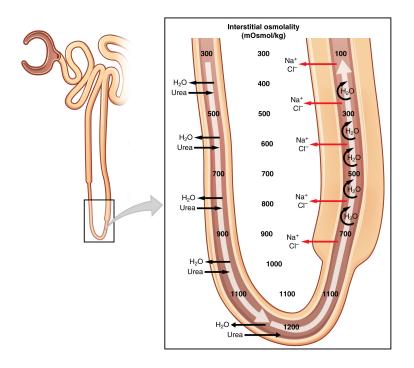
The ascending loop is made of very short thin and longer thick portions. Once again, to simplify the function, this section only considers the thick portion. The thick portion is lined with simple cuboidal epithelium without a brush border. It is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly Na⁺, are actively pumped out of the loop by large quantities of the Na^{+/}K⁺ ATPase pump. This has two significant effects: Removal of Na⁺ while retaining water leads to a hypotonic filtrate by the time it reaches the DCT; pumping Na⁺ into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The Na^{+/}K⁺ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of Cl⁻ by Na⁺/Cl⁻ symporters in the apical membrane. At the same time that Na⁺ is actively pumped from the basal side of the cell into the interstitial fluid, Cl⁻ follows the Na⁺ from the lumen into the interstitial fluid by a paracellular route between cells through **leaky tight junctions**. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the K⁺ that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane. Note the environment now created in the interstitial space: With the "back door exiting" K⁺, there is one Na⁺ and two Cl⁻ ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the lumen of the loop, the interstitial space is now a negatively charged environment. This negative charge attracts cations (Na⁺, K⁺, Ca⁺⁺, and Mg⁺⁺) from the lumen via a paracellular route to the interstitial space and vasa recta.

Countercurrent Multiplier System

The structure of the loop of Henle and associated vasa recta create a **countercurrent multiplier system** ([link]). The countercurrent term comes from the fact that the descending and ascending loops are next to each other and their fluid flows in opposite directions (countercurrent). The multiplier term is due to the action of solute pumps that increase (multiply) the concentrations of urea and Na⁺ deep in the medulla.

Countercurrent Multiplier System



As discussed above, the ascending loop has many Na⁺ pumps that actively pump Na⁺ out of the forming urine into the interstitial spaces. In addition, collecting ducts have urea pumps that actively pump urea into the interstitial spaces. This results in the recovery of Na⁺ to the circulation via the vasa recta and creates a high osmolar environment in the depths of the medulla.

Ammonia (NH_3) is a toxic byproduct of protein metabolism. It is formed as amino acids are deaminated by liver hepatocytes. That means that the amine group, NH_2 , is removed from amino acids as they are broken down. Most of the resulting ammonia is converted into urea by liver hepatocytes. Urea is not only less toxic but is utilized to aid in the recovery of water by the loop of Henle and collecting ducts. At the same time that water is freely diffusing out of the descending loop through aquaporin channels into the interstitial spaces of the medulla, urea freely diffuses into the lumen of the descending loop as it descends deeper into the medulla, much of it to be reabsorbed from the forming urine when it reaches the collecting duct. Thus, the movement of Na^+ and urea into the interstitial spaces by these mechanisms creates the hyperosmotic environment of the medulla. The net result of this countercurrent multiplier system is to recover both water and Na^+ in the circulation.

The amino acid glutamine can be deaminated by the kidney. As NH_2 from the amino acid is converted into NH_3 and pumped into the lumen of the PCT, Na^+ and HCO_3^- are excreted into the interstitial fluid of the renal pyramid via a symport mechanism. When this process occurs in the cells of the PCT, the added benefit is a net loss of a hydrogen ion (complexed to ammonia to form the weak acid NH_4^+) in the urine and a gain of a bicarbonate ion (HCO_3^-) in the blood. Ammonia and bicarbonate are exchanged in a one-to-one ratio. This exchange is yet another means by which the body can buffer and excrete acid. The presence of aquaporin channels in the descending loop allows prodigious quantities of water to leave

the loop and enter the hyperosmolar interstitium of the pyramid, where it is returned to the circulation by the vasa recta. As the loop turns to become the ascending loop, there is an absence of aquaporin channels, so water cannot leave the loop. However, in the basal membrane of cells of the thick ascending loop, ATPase pumps actively remove Na^+ from the cell. A $Na^+/K^+/2Cl^-$ symporter in the apical membrane passively allows these ions to enter the cell cytoplasm from the lumen of the loop down a concentration gradient created by the pump. This mechanism works to dilute the fluid of the ascending loop ultimately to approximately 50-100 mOsmol/L.

At the transition from the DCT to the collecting duct, about 20 percent of the original water is still present and about 10 percent of the sodium. If no other mechanism for water reabsorption existed, about 20–25 liters of urine would be produced. Now consider what is happening in the adjacent capillaries, the vasa recta. They are recovering both solutes and water at a rate that preserves the countercurrent multiplier system. In general, blood flows slowly in capillaries to allow time for exchange of nutrients and wastes. In the vasa recta particularly, this rate of flow is important for two additional reasons. The flow must be slow to allow blood cells to lose and regain water without either crenating or bursting. Second, a rapid flow would remove too much Na⁺ and urea, destroying the osmolar gradient that is necessary for the recovery of solutes and water. Thus, by flowing slowly to preserve the countercurrent mechanism, as the vasa recta descend, Na⁺ and urea are freely able to enter the capillary, while water freely leaves; as they ascend, Na⁺ and urea are secreted into the surrounding medulla, while water reenters and is removed.

Note:



Watch this <u>video</u> to learn about the countercurrent multiplier system.

Reabsorption and Secretion in the Distal Convoluted Tubule

Approximately 80 percent of filtered water has been recovered by the time the dilute forming urine enters the DCT. The DCT will recover another 10–15 percent before the forming urine enters the collecting ducts. Aldosterone increases the amount of Na⁺/K⁺ ATPase in the basal membrane of the DCT and collecting duct. The movement of Na⁺ out of the lumen of the collecting duct creates a negative charge that promotes the movement of

Cl⁻ out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation.

Cells of the DCT also recover Ca⁺⁺ from the filtrate. Receptors for parathyroid hormone (PTH) are found in DCT cells and when bound to PTH, induce the insertion of calcium channels on their luminal surface. The channels enhance Ca⁺⁺ recovery from the forming urine. In addition, as Na⁺ is pumped out of the cell, the resulting electrochemical gradient attracts Ca⁺⁺ into the cell. Finally, calcitriol (1,25 dihydroxyvitamin D, the active form of vitamin D) is very important for calcium recovery. It induces the production of calciumbinding proteins that transport Ca⁺⁺ into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any Ca⁺⁺ not reabsorbed at this point is lost in the urine.

Collecting Ducts and Recovery of Water

Solutes move across the membranes of the collecting ducts, which contain two distinct cell types, principal cells and intercalated cells. A **principal cell** possesses channels for the recovery or loss of sodium and potassium. An **intercalated cell** secretes or absorbs acid or bicarbonate. As in other portions of the nephron, there is an array of micromachines (pumps and channels) on display in the membranes of these cells.

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is recovered, the collecting ducts play a major role in maintaining the body's normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts recover more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts recover less of the water, leading to concentration of the blood. Another way of saying this is: If plasma osmolarity rises, more water is recovered and urine volume decreases; if plasma osmolarity decreases, less water is recovered and urine volume increases. This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary. If plasma osmolarity decreases slightly, the opposite occurs.

When stimulated by ADH, aquaporin channels are inserted into the apical membrane of principal cells, which line the collecting ducts. As the ducts descend through the medulla, the osmolarity surrounding them increases (due to the countercurrent mechanisms described above). If aquaporin water channels are present, water will be osmotically pulled from the collecting duct into the surrounding interstitial space and into the peritubular capillaries. Therefore, the final urine will be more concentrated. If less ADH is secreted, fewer aquaporin channels are inserted and less water is recovered, resulting in dilute urine. By altering the number of aquaporin channels, the volume of water recovered or lost is altered. This, in turn, regulates the blood osmolarity, blood pressure, and osmolarity of the urine.

As Na⁺ is pumped from the forming urine, water is passively recaptured for the circulation; this preservation of vascular volume is critically important for the maintenance of a normal blood pressure. Aldosterone is secreted by the adrenal cortex in response to angiotensin II stimulation. As an extremely potent vasoconstrictor, angiotensin II functions immediately to increase blood pressure. By also stimulating aldosterone production, it provides a longer-lasting mechanism to support blood pressure by maintaining vascular volume (water recovery).

In addition to receptors for ADH, principal cells have receptors for the steroid hormone aldosterone. While ADH is primarily involved in the regulation of water recovery, aldosterone regulates Na^+ recovery. Aldosterone stimulates principal cells to manufacture luminal Na^+ and K^+ channels as well as Na^+/K^+ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more Na^+ is recovered from the forming urine and water follows the Na^+ passively. As the pump recovers Na^+ for the body, it is also pumping K^+ into the forming urine, since the pump moves K^+ in the opposite direction. When aldosterone decreases, more Na^+ remains in the forming urine and more K^+ is recovered in the circulation. Symport channels move Na^+ and Cl^- together. Still other channels in the principal cells secrete K^+ into the collecting duct in direct proportion to the recovery of Na^+ .

Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb K^+ and HCO_3^- while secreting H^+ . This function lowers the acidity of the plasma while increasing the acidity of the urine.

Chapter Review

The kidney regulates water recovery and blood pressure by producing the enzyme renin. It is renin that starts a series of reactions, leading to the production of the vasoconstrictor angiotensin II and the salt-retaining steroid aldosterone. Water recovery is also powerfully and directly influenced by the hormone ADH. Even so, it only influences the last 10 percent of water available for recovery after filtration at the glomerulus, because 90 percent of water is recovered before reaching the collecting ducts. Depending on the body's fluid status at any given time, the collecting ducts can recover none or almost all of the water reaching them.

Mechanisms of solute recovery include active transport, simple diffusion, and facilitated diffusion. Most filtered substances are reabsorbed. Urea, NH3, creatinine, and some drugs are filtered or secreted as wastes. H⁺ and HCO3⁻ are secreted or reabsorbed as needed to maintain acid—base balance. Movement of water from the glomerulus is primarily due to pressure, whereas that of peritubular capillaries and vasa recta is due to osmolarity and concentration gradients. The PCT is the most metabolically active part of the nephron and uses a wide array of protein micromachines to maintain homeostasis—symporters, antiporters, and ATPase active transporters—in conjunction with diffusion, both simple and facilitated. Almost 100 percent of glucose, amino acids, and vitamins are recovered in the PCT. Bicarbonate (HCO3⁻) is recovered using the same enzyme, carbonic anhydrase (CA),

found in erythrocytes. The recovery of solutes creates an osmotic gradient to promote the recovery of water. The descending loop of the juxtaglomerular nephrons reaches an osmolarity of up to 1200 mOsmol/kg, promoting the recovery of water. The ascending loop is impervious to water but actively recovers Na⁺, reducing filtrate osmolarity to 50–100 mOsmol/kg. The descending and ascending loop and vasa recta form a countercurrent multiplier system to increase Na⁺ concentration in the kidney medulla. The collecting ducts actively pump urea into the medulla, further contributing to the high osmotic environment. The vasa recta recover the solute and water in the medulla, returning them to the circulation. Nearly 90 percent of water is recovered before the forming urine reaches the DCT, which will recover another 10 percent. Calcium recovery in the DCT is influenced by PTH and active vitamin D. In the collecting ducts, ADH stimulates aquaporin channel insertion to increase water recovery and thereby regulate osmolarity of the blood. Aldosterone stimulates Na⁺ recovery by the collecting duct.

Glossary

countercurrent multiplier system

involves the descending and ascending loops of Henle directing forming urine in opposing directions to create a concentration gradient when combined with variable permeability and sodium pumping

glycosuria

presence of glucose in the urine; caused by high blood glucose levels that exceed the ability of the kidneys to reabsorb the glucose; usually the result of untreated or poorly controlled diabetes mellitus

intercalated cell

specialized cell of the collecting ducts that secrete or absorb acid or bicarbonate; important in acid—base balance

leaky tight junctions

tight junctions in which the sealing strands of proteins between the membranes of adjacent cells are fewer in number and incomplete; allows limited intercellular movement of solvent and solutes

principal cell

found in collecting ducts and possess channels for the recovery or loss of sodium and potassium; under the control of aldosterone; also have aquaporin channels under ADH control to regulate recovery of water

OU Human Physiology: Regulation of Renal Blood Flow By the end of this section, you will be able to:

- Describe the myogenic and tubuloglomerular feedback mechanisms and explain how they affect urine volume and composition
- Describe the function of the juxtaglomerular apparatus and how it regulates glomerular filtration rate

It is vital that the flow of blood through the kidney be at a suitable rate to allow for filtration. This rate determines how much solute is retained or discarded, how much water is retained or discarded, and ultimately, the osmolarity of blood and the blood pressure of the body. Renal blood flow is extrinsically and intrinsically regulated. Extrinsically via the sympathetic nerves and intrinsically via myogenic and tubuloglomerular feedback mechanisms.

Sympathetic Nerves

The kidneys are innervated by the sympathetic neurons of the autonomic nervous system via the celiac plexus and splanchnic nerves. Reduction of sympathetic stimulation results in vasodilation and increased blood flow through the kidneys during resting conditions. When the frequency of action potentials increases, the arteriolar smooth muscle constricts (vasoconstriction), resulting in diminished glomerular flow, so less filtration occurs. Under conditions of stress, sympathetic nervous activity increases, resulting in the direct vasoconstriction of afferent arterioles (norepinephrine effect) as well as stimulation of the adrenal medulla. The adrenal medulla, in turn, produces a generalized vasoconstriction through the release of epinephrine. This includes vasoconstriction of the afferent arterioles, further reducing the volume of blood flowing through the kidneys. This process redirects blood to other organs with more immediate needs. If blood pressure falls, the sympathetic nerves will also stimulate the release of renin. Additional renin increases production of the powerful vasoconstrictor angiotensin II. Angiotensin II, as discussed above, will also stimulate aldosterone production to augment blood volume through retention of more Na⁺ and water. Only a 10 mm Hg pressure differential across the glomerulus is required for normal GFR, so very small changes in afferent arterial pressure significantly increase or decrease GFR.

Autoregulation

The kidneys are very effective at regulating the rate of blood flow over a wide range of blood pressures. Your blood pressure will decrease when you are relaxed or sleeping. It will increase when exercising. Yet, despite these changes, the filtration rate through the kidney will change very little. This is due to two internal autoregulatory mechanisms that operate without outside influence: the myogenic mechanism and the tubuloglomerular feedback mechanism.

Arteriole Myogenic Mechanism

The **myogenic mechanism** regulating blood flow within the kidney depends upon a characteristic shared by most smooth muscle cells of the body. When you stretch a smooth muscle cell, it contracts; when you stop, it relaxes, restoring its resting length. This mechanism works in the afferent arteriole that supplies the glomerulus. When blood pressure increases, smooth muscle cells in the wall of the arteriole are stretched and respond by contracting to resist the pressure, resulting in little change in flow. When blood pressure drops, the same smooth muscle cells relax to lower resistance, allowing a continued even flow of blood.

Tubuloglomerular Feedback

The **tubuloglomerular feedback** mechanism involves the JGA and a paracrine signaling mechanism utilizing ATP, adenosine, and nitric oxide (NO). This mechanism stimulates either contraction or relaxation of afferent arteriolar smooth muscle cells ([link]). Recall that the DCT is in intimate contact with the afferent and efferent arterioles of the glomerulus. Specialized macula densa cells in this segment of the tubule respond to changes in the fluid flow rate and Na⁺ concentration. As GFR increases,

there is less time for NaCl to be reabsorbed in the PCT, resulting in higher osmolarity in the filtrate. The increased fluid movement more strongly deflects single nonmotile cilia on macula densa cells. This increased osmolarity of the forming urine, and the greater flow rate within the DCT, activates macula densa cells to respond by releasing ATP and adenosine (a metabolite of ATP). ATP and adenosine act locally as paracrine factors to stimulate the myogenic juxtaglomerular cells of the afferent arteriole to constrict, slowing blood flow and reducing GFR. Conversely, when GFR decreases, less Na⁺ is in the forming urine, and most will be reabsorbed before reaching the macula densa, which will result in decreased ATP and adenosine, allowing the afferent arteriole to dilate and increase GFR. NO has the opposite effect, relaxing the afferent arteriole at the same time ATP and adenosine are stimulating it to contract. Thus, NO fine-tunes the effects of adenosine and ATP on GFR.

Paracrine Mechanisms Controlling Glomerular Filtration Rate						
Change in GFR	NaCl Absorption	Role of ATP and adenosine/Role of NO	Effect on GFR			
Increased GFR	Tubular NaCl increases	ATP and adenosine increase, causing vasoconstriction	Vasoconstriction slows GFR			

Paracrine Mechanisms Controlling Glomerular Filtration Rate					
Change in GFR	NaCl Absorption	Role of ATP and adenosine/Role of NO	Effect on GFR		
Decreased GFR	Tubular NaCl decreases	ATP and adenosine decrease, causing vasodilation	Vasodilation increases GFR		
Increased GFR	Tubular NaCl increases	NO increases, causing vasodilation	Vasodilation increases GFR		
Decreased GFR	Tubular NaCl decreases	NO decreases, causing vasoconstricton	Vasoconstriction decreases GFR		

Chapter Review

The kidneys are innervated by sympathetic nerves of the autonomic nervous system. Sympathetic nervous activity decreases blood flow to the kidney, making more blood available to other areas of the body during times of stress. The arteriolar myogenic mechanism maintains a steady blood flow by causing arteriolar smooth muscle to contract when blood pressure increases and causing it to relax when blood pressure decreases. Tubuloglomerular feedback involves paracrine signaling at the JGA to cause vasoconstriction or vasodilation to maintain a steady rate of blood flow.

Glossary

myogenic mechanism

mechanism by which smooth muscle responds to stretch by contracting; an increase in blood pressure causes vasoconstriction and a decrease in blood pressure causes vasodilation so that blood flow downstream remains steady

tubuloglomerular feedback

feedback mechanism involving the JGA; macula densa cells monitor Na⁺ concentration in the terminal portion of the ascending loop of Henle and act to cause vasoconstriction or vasodilation of afferent and efferent arterioles to alter GFR

OU Human Physiology: Endocrine Regulation of Kidney Function By the end of this section, you will be able to:

- Describe how each of the following functions in the extrinsic control of GFR: renin-angiotensin mechanism, natriuretic peptides, and sympathetic adrenergic activity
- Describe how each of the following works to regulate reabsorption and secretion so as to affect urine volume and composition: reninangiotensin system, aldosterone, ADH, and natriuretic peptides
- Name and define the roles of other hormones that regulate kidney control

Several hormones have specific, important roles in regulating kidney function. They act to stimulate or inhibit blood flow. Some of these are endocrine, acting from a distance, whereas others are paracrine, acting locally.

Renin-Angiotensin-Aldosterone

Renin is an enzyme that is produced by the granular cells of the afferent arteriole at the JGA. It enzymatically converts angiotensinogen (made by the liver, freely circulating) into angiotensin I. Its release is stimulated by prostaglandins and NO from the JGA in response to decreased extracellular fluid volume.

Antiotensin converting enzyme (ACE) is not a hormone but it is functionally important in regulating systemic blood pressure and kidney function. It is produced in the lungs but binds to the surfaces of endothelial cells in the afferent arterioles and glomerulus. It enzymatically converts inactive angiotensin I into active angiotensin II. ACE is important in raising blood pressure. People with high blood pressure are sometimes prescribed ACE inhibitors to lower their blood pressure.

Angiotensin II is a potent vasoconstrictor that plays an immediate role in the regulation of blood pressure. It acts systemically to cause vasoconstriction as well as constriction of both the afferent and efferent arterioles of the glomerulus. In instances of blood loss or dehydration, it reduces both GFR and renal blood flow, thereby limiting fluid loss and preserving blood volume. Its release is usually stimulated by decreases in blood pressure, and so the preservation of adequate blood pressure is its primary role.

Aldosterone, often called the "salt-retaining hormone," is released from the adrenal cortex in response to angiotensin II or directly in response to increased plasma K⁺. It promotes Na⁺ reabsorption by the nephron, promoting the retention of water. It is also important in regulating K^+ , promoting its excretion. (This dual effect on two minerals and its origin in the adrenal cortex explains its designation as a mineralocorticoid.) As a result, renin has an immediate effect on blood pressure due to angiotensin II–stimulated vasoconstriction and a prolonged effect through Na⁺ recovery due to aldosterone. At the same time that aldosterone causes increased recovery of Na⁺, it also causes greater loss of K⁺. Progesterone is a steroid that is structurally similar to aldosterone. It binds to the aldosterone receptor and weakly stimulates Na⁺ reabsorption and increased water recovery. This process is unimportant in men due to low levels of circulating progesterone. It may cause increased retention of water during some periods of the menstrual cycle in women when progesterone levels increase.

Antidiuretic Hormone (ADH)

Diuretics are drugs that can increase water loss by interfering with the recapture of solutes and water from the forming urine. They are often prescribed to lower blood pressure. Coffee, tea, and alcoholic beverages are familiar diuretics. ADH, a neuropeptide hormone released by the posterior pituitary, works to do the exact opposite. It promotes the recovery of water, decreases urine volume, and maintains plasma osmolarity and blood pressure. It does so by stimulating the movement of aquaporin proteins into the apical cell membrane of the late distal convoluted tubules and collecting ducts to form water channels, allowing the transcellular movement of water from the lumen of the collecting duct into the interstitial space in the medulla of the kidney by osmosis. From there, it enters the vasa recta capillaries to return to the circulation. Water is attracted by the high osmotic environment of the deep kidney medulla.

Endothelin

Endothelins are extremely powerful vasoconstrictors. They are produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT. Hormones stimulating endothelin release include angiotensin II, bradykinin, and epinephrine. They do not typically influence blood pressure in healthy people. On the other hand, in people with diabetic kidney disease, endothelin is chronically elevated, resulting in sodium retention. They also diminish GFR by damaging the podocytes and by potently vasoconstricting both the afferent and efferent arterioles.

Natriuretic Hormones

Natriuretic hormones are peptides that stimulate the kidneys to excrete sodium—an effect opposite that of aldosterone. Natriuretic hormones act by inhibiting aldosterone release and therefore inhibiting Na⁺ recovery in the collecting ducts. If Na⁺ remains in the forming urine, its osmotic force will cause a concurrent loss of water. Natriuretic hormones also inhibit ADH release, which of course will result in less water recovery. Therefore, natriuretic peptides inhibit both Na⁺ and water recovery. One example from this family of hormones is atrial natriuretic hormone (ANH), a peptide produced by heart atria in response to over-stretching of the atrial wall. The over-stretching occurs in persons with elevated blood pressure or heart failure. It increases GFR through concurrent vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole. These events lead to an increased loss of water and sodium in the forming urine. It also decreases sodium reabsorption in the DCT. There is also B-type natriuretic peptide (BNP) produced in the ventricles of the heart. It has a 10-fold lower affinity for its receptor, so its effects are less than those of ANH. Its role may be to provide "fine tuning" for the regulation of blood pressure. BNP's longer biologic half-life makes it a good diagnostic marker of congestive heart failure ([link]).

Parathyroid Hormone

Parathyroid hormone (PTH) is a peptide produced by the parathyroid glands in response to decreased circulating Ca^{++} levels. Among its targets is the PCT, where it stimulates the hydroxylation of calcidiol to calcitriol (1,25-hydroxycholecalciferol, the active form of vitamin D). It also blocks reabsorption of phosphate (PO_3^-), causing its loss in the urine. The retention of phosphate would result in the formation of calcium phosphate in the plasma, reducing circulating Ca^{++} levels. By ridding the blood of phosphate, higher circulating Ca^{++} levels are permitted.

Major Hormones That Influence GFR and RFB

	Stimulus	Effect on GFR	Effect on RBF			
VASOCONSTRICTORS						
Sympathetic nerves (epinephrine and norepinephrine)	↓ECFV	↓	†			
Angiotensin II	↓ ECFV	+	+			
Endothelin	↑ Stretch, bradykinin, angiotensin II, epinephrine ↓ ECFV	+	ţ			
VASODILATORS						
Prostaglandins (PGE1, PGE2, and PGI2)	↓ECFV shear stress, angiotensin II	No change/ ₱	f			
Nitric oxide (NO)	shear stress, acetylcholine, histamine, bradykinin, ATP, adenosine	†	t			
Bradykinin	Prostaglandins, ↓ ACE	t	f			
Natriuretic peptides (ANP, B-type)	† ECFV	t	No change			
ACE angietanein conver	ting onzymo: ECEV – ovtracelly	lar fluid valumas C	ED – alomorulor			

ACE = angiotensin-converting enzyme; ECFV = extracellular fluid volume; GFR = glomerular filtration rate; RBF = renal blood flow; ANP = atrial natriuretic peptide; B-type = ventricular natriuretic peptide

Chapter Review

Endocrine hormones act from a distance and paracrine hormones act locally. The renal enzyme renin converts angiotensinogen into angiotensin I. The lung enzyme, ACE, converts angiotensin I into active angiotensin II. Angiotensin II is an active vasoconstrictor that increases blood pressure. Angiotensin II also stimulates aldosterone release from the adrenal cortex, causing the collecting duct to retain Na⁺, which promotes water retention and a longer-term rise in blood pressure. ADH promotes water recovery by the collecting ducts by stimulating the insertion of aquaporin water channels into cell membranes. Endothelins are elevated in cases of diabetic

kidney disease, increasing Na⁺ retention and decreasing GFR. Natriuretic hormones, released primarily from the atria of the heart in response to stretching of the atrial walls, stimulate Na⁺ excretion and thereby decrease blood pressure. PTH stimulates the final step in the formation of active vitamin D3 and reduces phosphate reabsorption, resulting in higher circulating Ca⁺⁺ levels.

Glossary

endothelins

group of vasoconstrictive, 21-amino acid peptides; produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT

OU Human Physiology: Regulation of Fluid Volume and Composition By the end of this section, you will be able to:

- Discuss how blood pressure reflects blood volume and is measured by baroreceptors and how this may trigger a sympathetic response
- Describe the relationship between the baroreceptors and the reninangiotensin system
- Describe the effect of a diuretic on urine volume and therefore blood volume
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation

The major hormones influencing total body water are ADH, aldosterone, and ANH. Circumstances that lead to fluid depletion in the body include blood loss and dehydration. Homeostasis requires that volume and osmolarity be preserved. Blood volume is important in maintaining sufficient blood pressure, and there are nonrenal mechanisms involved in its preservation, including vasoconstriction, which can act within seconds of a drop in pressure. Thirst mechanisms are also activated to promote the consumption of water lost through respiration, evaporation, or urination. Hormonal mechanisms are activated to recover volume while maintaining a normal osmotic environment. These mechanisms act principally on the kidney.

Volume-sensing Mechanisms

The body cannot directly measure blood volume, but blood pressure can be measured. Blood pressure often reflects blood volume and is measured by baroreceptors in the aorta and carotid sinuses. When blood pressure increases, baroreceptors send more frequent action potentials to the central nervous system, leading to widespread vasodilation. Included in this vasodilation are the afferent arterioles supplying the glomerulus, resulting in increased GFR, and water loss by the kidneys. If pressure decreases, fewer action potentials travel to the central nervous system, resulting in more sympathetic stimulation-producing vasoconstriction, which will result in decreased filtration and GFR, and water loss.

Decreased blood pressure is also sensed by the granular cells in the afferent arteriole of the JGA. In response, the enzyme renin is released. You saw earlier in the chapter that renin activity leads to an almost immediate rise in blood pressure as activated angiotensin II produces vasoconstriction. The rise in pressure is sustained by the aldosterone effects initiated by angiotensin II; this includes an increase in Na⁺ retention and water volume. As an aside, late in the menstrual cycle, progesterone has a modest influence on water retention. Due to its structural similarity to aldosterone, progesterone binds to the aldosterone receptor in the collecting duct of the kidney, causing the same, albeit weaker, effect on Na⁺ and water retention.

Cardiomyocytes of the atria also respond to greater stretch (as blood pressure rises) by secreting ANH. ANH opposes the action of aldosterone by inhibiting the recovery of Na⁺ by the DCT and collecting ducts. More Na⁺ is lost, and as water follows, total blood volume and pressure decline. In low-pressure states, ANH does not seem to have much effect.

ADH is also called vasopressin. Early researchers found that in cases of unusually high secretion of ADH, the hormone caused vasoconstriction (vasopressor activity, hence the name). Only later were its antidiuretic properties identified. Synthetic ADH is still used occasionally to stem lifethreatening esophagus bleeding in alcoholics.

When blood volume drops 5–10 percent, causing a decrease in blood pressure, there is a rapid and significant increase in ADH release from the posterior pituitary. Immediate vasoconstriction to increase blood pressure is the result. ADH also causes activation of aquaporin channels in the collecting ducts to affect the recovery of water to help restore vascular volume.

Diuretics and Fluid Volume

A **diuretic** is a compound that increases urine volume. Three familiar drinks contain diuretic compounds: coffee, tea, and alcohol. The caffeine in coffee and tea works by promoting vasodilation in the nephron, which increases GFR. Alcohol increases GFR by inhibiting ADH release from the posterior pituitary, resulting in less water recovery by the collecting duct. In

cases of high blood pressure, diuretics may be prescribed to reduce blood volume and, thereby, reduce blood pressure. The most frequently prescribed anti-hypertensive diuretic is hydrochlorothiazide. It inhibits the Na⁺/ Cl⁻ symporter in the DCT and collecting duct. The result is a loss of Na⁺ with water following passively by osmosis.

Osmotic diuretics promote water loss by osmosis. An example is the indigestible sugar mannitol, which is most often administered to reduce brain swelling after head injury. However, it is not the only sugar that can produce a diuretic effect. In cases of poorly controlled diabetes mellitus, glucose levels exceed the capacity of the tubular glucose symporters, resulting in glucose in the urine. The unrecovered glucose becomes a powerful osmotic diuretic. Classically, in the days before glucose could be detected in the blood and urine, clinicians identified diabetes mellitus by the three Ps: polyuria (diuresis), polydipsia (increased thirst), and polyphagia (increased hunger).

Regulation of Extracellular Na⁺

Sodium has a very strong osmotic effect and attracts water. It plays a larger role in the osmolarity of the plasma than any other circulating component of the blood. If there is too much Na⁺ present, either due to poor control or excess dietary consumption, a series of metabolic problems ensue. There is an increase in total volume of water, which leads to hypertension (high blood pressure). Over a long period, this increases the risk of serious complications such as heart attacks, strokes, and aneurysms. It can also contribute to system-wide edema (swelling).

Mechanisms for regulating Na⁺ concentration include the renin—angiotensin—aldosterone system and ADH (see [link]). Aldosterone stimulates the uptake of Na⁺ on the apical cell membrane of cells in the DCT and collecting ducts, whereas ADH helps to regulate Na⁺ concentration indirectly by regulating the reabsorption of water.

Regulation of Extracellular K⁺

Potassium is present in a 30-fold greater concentration inside the cell than outside the cell. A generalization can be made that K^+ and Na^+ concentrations will move in opposite directions. When more Na^+ is reabsorbed, more K^+ is secreted; when less Na^+ is reabsorbed (leading to excretion by the kidney), more K^+ is retained. When aldosterone causes a recovery of Na^+ in the nephron, a negative electrical gradient is created that promotes the secretion of K^+ and Cl^- into the lumen.

Regulation of Cl

Chloride is important in acid—base balance in the extracellular space and has other functions, such as in the stomach, where it combines with hydrogen ions in the stomach lumen to form hydrochloric acid, aiding digestion. Its close association with Na⁺ in the extracellular environment makes it the dominant anion of this compartment, and its regulation closely mirrors that of Na⁺.

Regulation of Ca++ and Phosphate

The parathyroid glands monitor and respond to circulating levels of Ca⁺⁺ in the blood. When levels drop too low, PTH is released to stimulate the DCT to reabsorb Ca⁺⁺ from the forming urine. When levels are adequate or high, less PTH is released and more Ca⁺⁺ remains in the forming urine to be lost. Phosphate levels move in the opposite direction. When Ca⁺⁺ levels are low, PTH inhibits reabsorption of so that its blood level drops, allowing Ca⁺⁺ levels to rise. PTH also stimulates the renal conversion of calcidiol into calcitriol, the active form of vitamin D. Calcitriol then stimulates the intestines to absorb more Ca⁺⁺ from the diet.

Regulation of H⁺, Bicarbonate, and pH

The acid—base homeostasis of the body is a function of chemical buffers and physiologic buffering provided by the lungs and kidneys. Buffers, especially proteins, , and ammonia have a very large capacity to absorb or release H⁺ as needed to resist a change in pH. They can act within fractions of a second. The lungs can rid the body of excess acid very rapidly

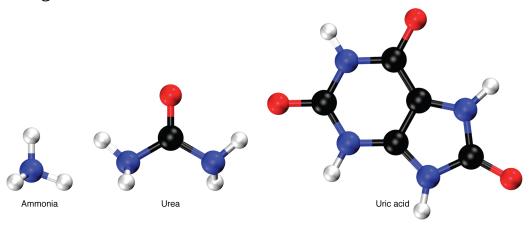
(seconds to minutes) through the conversion of HCO_3^- into CO_2 , which is then exhaled. It is rapid but has limited capacity in the face of a significant acid challenge. The kidneys can rid the body of both acid and base. The renal capacity is large but slow (minutes to hours). The cells of the PCT actively secrete H^+ into the forming urine as Na^+ is reabsorbed. The body rids itself of excess H^+ and raises blood pH. In the collecting ducts, the apical surfaces of intercalated cells have proton pumps that actively secrete H^+ into the luminal, forming urine to remove it from the body.

As hydrogen ions are pumped into the forming urine, it is buffered by bicarbonate (HCO_3^-), $H_2PO_4^-$ (dihydrogen phosphate ion), or ammonia (forming NH_4^+ , ammonium ion). Urine pH typically varies in a normal range from 4.5 to 8.0.

Regulation of Nitrogen Wastes

Nitrogen wastes are produced by the breakdown of proteins during normal metabolism. Proteins are broken down into amino acids, which in turn are deaminated by having their nitrogen groups removed. Deamination converts the amino (NH₂) groups into ammonia (NH₃), ammonium ion (NH₄ $^+$), urea, or uric acid ([link]). Ammonia is extremely toxic, so most of it is very rapidly converted into urea in the liver. Human urinary wastes typically contain primarily urea with small amounts of ammonium and very little uric acid.

Nitrogen Wastes



Elimination of Drugs and Hormones

Water-soluble drugs may be excreted in the urine and are influenced by one or all of the following processes: glomerular filtration, tubular secretion, or tubular reabsorption. Drugs that are structurally small can be filtered by the glomerulus with the filtrate. Large drug molecules such as heparin or those that are bound to plasma proteins cannot be filtered and are not readily eliminated. Some drugs can be eliminated by carrier proteins that enable secretion of the drug into the tubule lumen. There are specific carriers that eliminate basic (such as dopamine or histamine) or acidic drugs (such as penicillin or indomethacin). As is the case with other substances, drugs may be both filtered and reabsorbed passively along a concentration gradient.

Chapter Review

The major hormones regulating body fluids are ADH, aldosterone and ANH. Progesterone is similar in structure to aldosterone and can bind to and weakly stimulate aldosterone receptors, providing a similar but diminished response. Blood pressure is a reflection of blood volume and is monitored by baroreceptors in the aortic arch and carotid sinuses. When blood pressure increases, more action potentials are sent to the central nervous system, resulting in greater vasodilation, greater GFR, and more water lost in the urine. ANH is released by the cardiomyocytes when blood pressure increases, causing Na⁺ and water loss. ADH at high levels causes vasoconstriction in addition to its action on the collecting ducts to recover more water. Diuretics increase urine volume. Mechanisms for controlling Na⁺ concentration in the blood include the renin–angiotensin–aldosterone system and ADH. When Na⁺ is retained, K⁺ is excreted; when Na⁺ is lost, K⁺ is retained. When circulating Ca⁺⁺ decreases, PTH stimulates the reabsorption of Ca⁺⁺ and inhibits reabsorption of . pH is regulated through buffers, expiration of CO₂, and excretion of acid or base by the kidneys. The breakdown of amino acids produces ammonia. Most ammonia is converted into less-toxic urea in the liver and excreted in the urine. Regulation of drugs is by glomerular filtration, tubular secretion, and tubular reabsorption.

Glossary

diuretic

compound that increases urine output, leading to decreased water conservation

OU Human Physiology: The Urinary System and Homeostasis By the end of this section, you will be able to:

- Describe the role of the kidneys in regulating erythropoiesis
- Provide specific examples to demonstrate how the urinary system responds to maintain homeostasis in the body
- Explain how the urinary system relates to other body systems in maintaining homeostasis
- Predict factors or situations affecting the urinary system that could disrupt homeostasis
- Predict the types of problems that would occur in the body if the urinary system could not maintain homeostasis

All systems of the body are interrelated. A change in one system may affect all other systems in the body, with mild to devastating effects. A failure of urinary continence can be embarrassing and inconvenient, but is not life threatening. The loss of other urinary functions may prove fatal. A failure to synthesize vitamin D is one such example.

Vitamin D Synthesis

In order for vitamin D to become active, it must undergo a hydroxylation reaction in the kidney, that is, an –OH group must be added to calcidiol to make calcitriol (1,25-dihydroxycholecalciferol). Activated vitamin D is important for absorption of Ca⁺⁺ in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of Ca⁺⁺ and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate Ca⁺⁺ leads to disorders like osteoporosis and **osteomalacia** in adults and rickets in children. Deficits may also result in problems with cell proliferation, neuromuscular function, blood clotting, and the inflammatory response. Recent research has confirmed that vitamin D receptors are present in most, if not all, cells of the body, reflecting the systemic importance of vitamin D. Many scientists have suggested it be referred to as a hormone rather than a vitamin.

Erythropoiesis

EPO is a 193-amino acid protein that stimulates the formation of red blood cells in the bone marrow. The kidney produces 85 percent of circulating EPO; the liver, the remainder. If you move to a higher altitude, the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell. One way the body compensates is to manufacture more red blood cells by increasing EPO production. If you start an aerobic exercise program, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under produced due to disease or severe malnutrition, the kidneys come to the rescue by producing more EPO. Renal failure (loss of EPO production) is associated with anemia, which makes it difficult for the body to cope with increased oxygen demands or to supply oxygen adequately even under normal conditions. Anemia diminishes performance and can be life threatening.

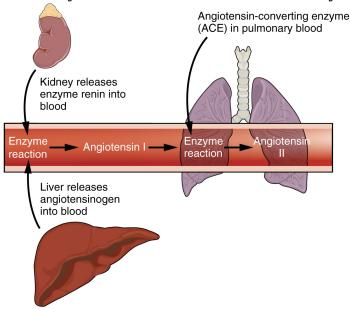
Blood Pressure Regulation

Due to osmosis, water follows where Na⁺ leads. Much of the water the kidneys recover from the forming urine follows the reabsorption of Na⁺. ADH stimulation of aquaporin channels allows for regulation of water recovery in the collecting ducts. Normally, all of the glucose is recovered, but loss of glucose control (diabetes mellitus) may result in an osmotic dieresis severe enough to produce severe dehydration and death. A loss of renal function means a loss of effective vascular volume control, leading to hypotension (low blood pressure) or hypertension (high blood pressure), which can lead to stroke, heart attack, and aneurysm formation.

The kidneys cooperate with the lungs, liver, and adrenal cortex through the renin—angiotensin—aldosterone system (see [link]). The liver synthesizes and secretes the inactive precursor angiotensinogen. When the blood pressure is low, the kidney synthesizes and releases renin. Renin converts angiotensinogen into angiotensin I, and ACE produced in the lung converts angiotensin I into biologically active angiotensin II ([link]). The immediate and short-term effect of angiotensin II is to raise blood pressure by causing widespread vasoconstriction. angiotensin II also stimulates the adrenal cortex to release the steroid hormone aldosterone, which results in renal

reabsorption of Na⁺ and its associated osmotic recovery of water. The reabsorption of Na⁺ helps to raise and maintain blood pressure over a longer term.

The Enzyme Renin Converts the Pro-enzyme Angiotensin



Regulation of Osmolarity

Blood pressure and osmolarity are regulated in a similar fashion. Severe hypo-osmolarity can cause problems like lysis (rupture) of blood cells or widespread edema, which is due to a solute imbalance. Inadequate solute concentration (such as protein) in the plasma results in water moving toward an area of greater solute concentration, in this case, the interstitial space and cell cytoplasm. If the kidney glomeruli are damaged by an autoimmune illness, large quantities of protein may be lost in the urine. The resultant drop in serum osmolarity leads to widespread edema that, if severe, may lead to damaging or fatal brain swelling. Severe hypertonic conditions may arise with severe dehydration from lack of water intake, severe vomiting, or uncontrolled diarrhea. When the kidney is unable to recover sufficient water from the forming urine, the consequences may be severe (lethargy, confusion, muscle cramps, and finally, death).

Recovery of Electrolytes

Sodium, calcium, and potassium must be closely regulated. The role of Na⁺ and Ca⁺⁺ homeostasis has been discussed at length. Failure of K⁺ regulation can have serious consequences on nerve conduction, skeletal muscle function, and most significantly, on cardiac muscle contraction and rhythm.

pH Regulation

Recall that enzymes lose their three-dimensional conformation and, therefore, their function if the pH is too acidic or basic. This loss of conformation may be a consequence of the breaking of hydrogen bonds. Move the pH away from the optimum for a specific enzyme and you may severely hamper its function throughout the body, including hormone binding, central nervous system signaling, or myocardial contraction. Proper kidney function is essential for pH homeostasis.

Note:

Everyday Connection

Stem Cells and Repair of Kidney Damage

Stem cells are unspecialized cells that can reproduce themselves via cell division, sometimes after years of inactivity. Under certain conditions, they may differentiate into tissue-specific or organ-specific cells with special functions. In some cases, stem cells may continually divide to produce a mature cell and to replace themselves. Stem cell therapy has an enormous potential to improve the quality of life or save the lives of people suffering from debilitating or life-threatening diseases. There have been several studies in animals, but since stem cell therapy is still in its infancy, there have been limited experiments in humans.

Acute kidney injury can be caused by a number of factors, including transplants and other surgeries. It affects 7–10 percent of all hospitalized patients, resulting in the deaths of 35–40 percent of inpatients. In limited studies using mesenchymal stem cells, there have been fewer instances of kidney damage after surgery, the length of hospital stays has been reduced, and there have been fewer readmissions after release.

How do these stem cells work to protect or repair the kidney? Scientists are unsure at this point, but some evidence has shown that these stem cells

release several growth factors in endocrine and paracrine ways. As further studies are conducted to assess the safety and effectiveness of stem cell therapy, we will move closer to a day when kidney injury is rare, and curative treatments are routine.

Chapter Review

The effects of failure of parts of the urinary system may range from inconvenient (incontinence) to fatal (loss of filtration and many others). The kidneys catalyze the final reaction in the synthesis of active vitamin D that in turn helps regulate Ca⁺⁺. The kidney hormone EPO stimulates erythrocyte development and promotes adequate O₂ transport. The kidneys help regulate blood pressure through Na⁺ and water retention and loss. The kidneys work with the adrenal cortex, lungs, and liver in the renin—angiotensin—aldosterone system to regulate blood pressure. They regulate osmolarity of the blood by regulating both solutes and water. Three electrolytes are more closely regulated than others: Na⁺, Ca⁺⁺, and K⁺. The kidneys share pH regulation with the lungs and plasma buffers, so that proteins can preserve their three-dimensional conformation and thus their function.

Glossary

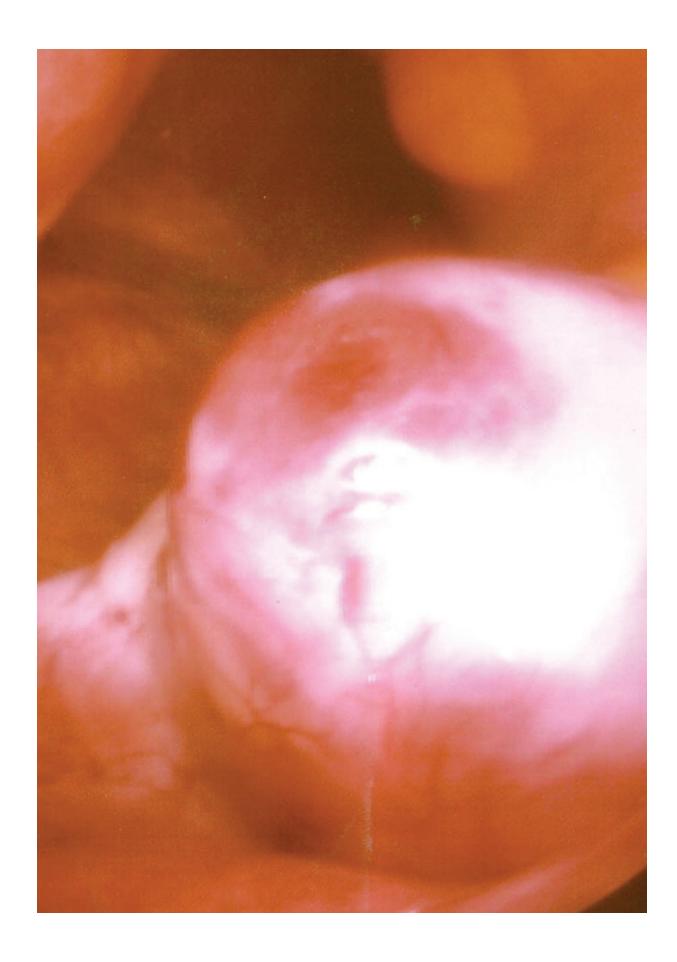
osteomalacia

softening of bones due to a lack of mineralization with calcium and phosphate; most often due to lack of vitamin D; in children, osteomalacia is termed rickets; not to be confused with osteoporosis

OU Human Physiology: The Reproductive System Introduction class="introduction" Ovulation

```
Following
a surge of
luteinizin
    g
hormone
(LH), an
 oocyte
(immature
egg cell)
 will be
 released
 into the
 uterine
  tube,
 where it
will then
   be
available
  to be
fertilized
  by a
 male's
 sperm.
Ovulation
marks the
end of the
follicular
phase of
   the
 ovarian
cycle and
 the start
  of the
```

luteal phase.



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the structure and function of the major and accessory organs of the male and female reproductive systems
- Explain the role of hypothalamic and pituitary hormones in male and female reproductive function
- Trace the path of a sperm cell from its initial production through fertilization of an oocyte
- Explain the events of spermatogenesis
- Explain the events in oogenesis through fertilization
- Describe the development and maturation of the sex organs and the emergence of secondary sex characteristics during puberty

Small, uncoordinated, and slick with amniotic fluid, a newborn encounters the world outside of her mother's womb. We do not often consider that a child's birth is proof of the healthy functioning of both her mother's and father's reproductive systems. Moreover, her parents' endocrine systems had to secrete the appropriate regulating hormones to induce the production and release of unique male and female gametes, reproductive cells containing the parents' genetic material (one set of 23 chromosomes). Her parent's reproductive behavior had to facilitate the transfer of male gametes —the sperm—to the female reproductive tract at just the right time to encounter the female gamete, an oocyte (egg). Finally, combination of the gametes (fertilization) had to occur, followed by implantation and development. In this chapter, you will explore the male and female reproductive systems, whose healthy functioning can culminate in the powerful sound of a newborn's first cry.

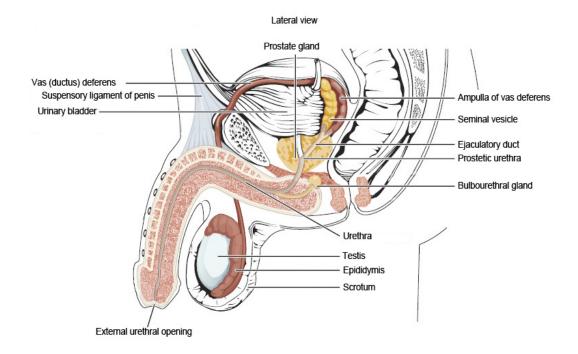
OU Human Physiology: Anatomy and Physiology of the Male Reproductive System

By the end of this section, you will be able to:

- Describe the structure and function of the major and accessory organs of the male reproductive system
- Explain the events during spermatogenesis that produce haploid sperm from diploid cells
- Describe the structure and function of the sperm cell
- Trace the path of spermatogonia to spermatozoa to the urethra and explain the process through which sperm are transported
- Describe the three phases of the sexual response in males
- Identify the importance of testosterone in male reproductive function
- Explain the role of hypothalamic and pituitary hormones in male reproductive function
- Describe how aging affects male reproduction

Unique for its role in human reproduction, a **gamete** is a specialized sex cell carrying 23 chromosomes—one half the number in body cells. At fertilization, the chromosomes in one male gamete, called a **sperm** (or spermatozoon), combine with the chromosomes in one female gamete, called an oocyte. The function of the male reproductive system ([link]) is to produce sperm and transfer them to the female reproductive tract. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support male reproductive physiology. In humans, the most important male androgen is testosterone. Several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which delivers sperm to the female reproductive tract. In this section, we examine each of these different structures, and discuss the process of sperm production and transport.

Male Reproductive System



The structures of the male reproductive system include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen.

Scrotum

The testes are located in a skin-covered, highly pigmented, muscular sack called the **scrotum** that extends from the body behind the penis (see [link]). This location is important in sperm production, which occurs within the testes, and proceeds more efficiently when the testes are kept 2 to 4°C below core body temperature.

The subcutaneous muscle layer of the scrotum makes up the scrotal septum, a wall that divides the scrotum into two compartments, each housing one testis ([link]). Descending from the internal oblique muscle of the abdominal wall are two muscles, which cover each testis like a muscular

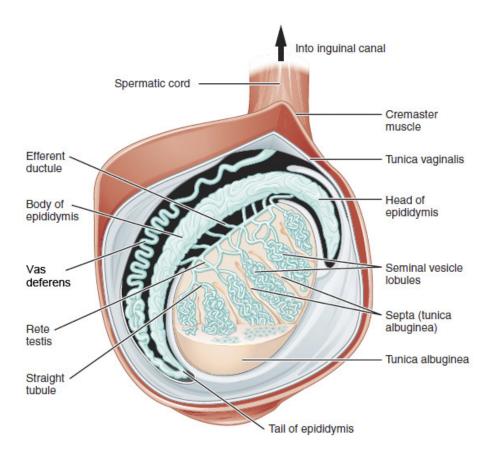
net. By contracting simultaneously, muscles can elevate the testes in cold weather (or water), moving the testes closer to the body and decreasing the surface area of the scrotum to retain heat. Alternatively, as the environmental temperature increases, the scrotum relaxes, moving the testes farther from the body core and increasing scrotal surface area, which promotes heat loss.

Testes

The **testes** (singular = testis) are the male **gonads**—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the male.

Paired ovals, the testes are each approximately 4 to 5 cm in length and are housed within the scrotum (see [link]). They are surrounded by two distinct layers of protective connective tissue, tunica vaginalis and tunica albuginea, a tough white, dense, connective tissue layer covering the testis itslf ([link]). Not only does the tunica albuginea cover the outside of the testis, it also invaginates to form septa that divide the testis into 300 to 400 structures called lobules. Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the "descent of the testis." Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum prior to birth.

Anatomy of the Testis



This sagittal view shows the seminiferous tubules, the site of sperm production. Formed sperm are transferred to the epididymis, where they mature. They leave the epididymis during an ejaculation via the ductus deferens.

The tightly coiled **seminiferous tubules** form the bulk of each testis. They are composed of developing sperm cells surrounding a lumen, the hollow center of the tubule, where formed sperm are released into the duct system of the testis. Specifically, from the lumens of the seminiferous tubules, sperm move into the straight tubules, and from there into a fine meshwork of tubules called the rete testes. Sperm leave the rete testes, and the testis itself, through the 15 to 20 efferent ductules that cross the tunica albuginea.

Inside the seminiferous tubules are six different cell types. These include supporting cells called Sertoli cells, as well as five types of developing

sperm cells called germ cells. Germ cell development progresses from the basement membrane—at the perimeter of the tubule—toward the lumen. Let's look more closely at these cell types.

Sertoli Cells

Surrounding all stages of the developing sperm cells are elongate, branching **Sertoli cells**. Sertoli cells are a type of supporting cell called a sustentacular cell, or sustenocyte, that are typically found in epithelial tissue. Sertoli cells secrete signaling molecules that promote spermatogenesis (sperm production) and can control whether germ cells live or die. They extend physically around the germ cells from the peripheral basement membrane of the seminiferous tubules to the lumen. Tight junctions between these cells create the **blood–testis barrier**, which keeps bloodborne substances from reaching the germ cells and, at the same time, keeps surface antigens on developing germ cells from escaping into the bloodstream and prompting an autoimmune response. Smooth muscle cells surrounding the basement membrane enable sperm transport through the seminiferous tubule via peristalsis.

Germ Cells

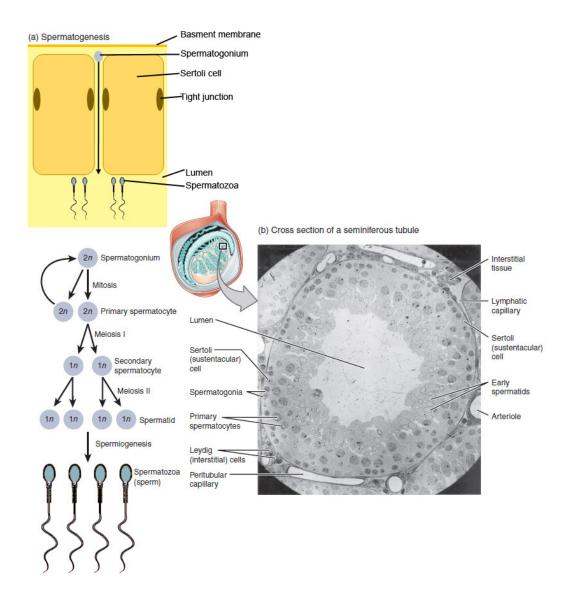
The least mature cells, the **spermatogonia** (singular = spermatogonium), line the basement membrane inside the tubule. Spermatogonia are the stem cells of the testis, which means that they are still able to differentiate into a variety of different cell types throughout adulthood. Spermatogonia divide to produce primary and secondary spermatocytes, then spermatids, which finally produce formed sperm. The process that begins with spermatogonia and concludes with the production of sperm is called **spermatogenesis**.

Spermatogenesis

As just noted, spermatogenesis occurs in the seminiferous tubules that form the bulk of each testis (see [link]). The process begins at puberty, after which time sperm are produced constantly throughout a man's life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days, although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a man produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.

The process of spermatogenesis begins with mitosis of the diploid spermatogonia between the Sertoli cells and near the basement membrane ([link]). Because these cells are diploid (2n), they each have a complete copy of the father's genetic material, or 46 chromosomes. However, mature gametes are haploid (1n), containing 23 chromosomes—meaning that daughter cells of spermatogonia must undergo a second cellular division through the process of meiosis.

Spermatogenesis



This process occurs between the Sertoli cells that are held together via tight junctions.(a) Mitosis of a spermatogonial stem cell involves a single cell division that results in two identical, diploid daughter cells (spermatogonia to primary spermatocyte). Meiosis has two rounds of cell division: primary spermatocyte to secondary spermatocyte, and then secondary spermatocyte to spermatid. This produces four haploid daughter cells (spermatids). This process begins near the basement membrane and continues until spermatozoa are produced and released in the lumen of the tubule. (b) In this electron micrograph of a cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of

the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

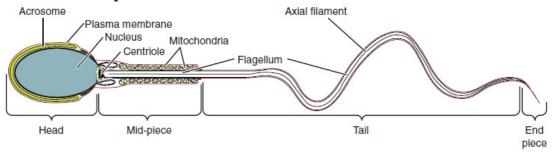
Two identical diploid cells result from spermatogonia mitosis. One of these cells remains a spermatogonium, and the other becomes a primary **spermatocyte**, the next stage in the process of spermatogenesis. The primary spermatocyte undergoes the first division of meiosis with each cell producing two secondary spermatocytes. Now a second round of meiosis occurs in both of the secondary spermatocytes, separating the chromosome pairs. This second meiotic division results in a total of four cells with only half of the number of chromosomes. Each of these new cells is a **spermatid**. Although haploid, early spermatids look very similar to cells in the earlier stages of spermatogenesis, with a round shape, central nucleus, and large amount of cytoplasm. A process called **spermiogenesis** transforms these early spermatids, reducing the cytoplasm, and beginning the formation of the parts of a true sperm. The fifth stage of germ cell formation—spermatozoa, or formed sperm—is the end result of this process, which occurs in the portion of the seminiferous tubule nearest the lumen. Eventually, the sperm are released into the lumen and are moved along a series of ducts in the testis toward a structure called the epididymis for the next step of sperm maturation.

Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the female gamete. Approximately 100 to 300 million sperm are produced each day, whereas women typically ovulate only one oocyte per month as is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region ([link]). The head of the sperm contains the extremely compact haploid nucleus with very little cytoplasm. These qualities contribute to the overall small size of the sperm

(the head is only 5 μ m long). A structure called the acrosome covers most of the head of the sperm cell as a "cap" that is filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed mitochondria fill the mid-piece of the sperm. ATP produced by these mitochondria will power the flagellum, which extends from the neck and the mid-piece through the tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.

Structure of Sperm



Sperm cells are divided into a head, containing DNA; a midpiece, containing mitochondria; and a tail, providing motility. The acrosome is oval and somewhat flattened.

Sperm Transport

To fertilize an egg, sperm must be moved from the seminiferous tubules in the testes, through the epididymis, and—later during ejaculation—along the length of the penis and out into the female reproductive tract.

Role of the Epididymis

From the lumen of the seminiferous tubules, the immotile sperm are surrounded by testicular fluid and moved through the rete testis into the efferent ductules to the **epididymis** (plural = epididymides), a coiled tube

attached to the testis where newly formed sperm continue to mature (see [link]). Though the epididymis does not take up much room in its tightly coiled state, it would be approximately 6 m (20 feet) long if straightened. It takes an average of 12 days for sperm to move through the coils of the epididymis, with the shortest recorded transit time in humans being one day. Sperm enter the head of the epididymis and are moved along predominantly by the contraction of smooth muscles lining the epididymal tubes. As they are moved along the length of the epididymis, the sperm further mature and acquire the ability to move under their own power. Once inside the female reproductive tract, they will use this ability to move independently toward the unfertilized egg. The more mature sperm are then stored in the tail of the epididymis (the final section) until ejaculation occurs.

Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the **vas deferens** (also called the ductus deferens). The vas deferens is a thick, muscular tube that is bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the spermatic cord. Because the vas deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the vas deferens. This procedure is called a vasectomy, and it is an effective form of male birth control. Although it may be possible to reverse a vasectomy, clinicians consider the procedure permanent, and advise men to undergo it only if they are certain they no longer wish to father children.

Note: Interactive Link Feature



Watch this <u>video</u> to learn about a vasectomy. As described in this video, a vasectomy is a procedure in which a small section of the ductus (vas) deferens is removed from the scrotum. This interrupts the path taken by sperm through the ductus deferens. If sperm do not exit through the vas, either because the man has had a vasectomy or has not ejaculated, in what region of the testis do they remain?

From each epididymis, each vas deferens extends superiorly into the abdominal cavity through the inguinal canal in the abdominal wall. From here, the vas deferens continues posteriorly to the pelvic cavity, ending posterior to the bladder where it dilates in a region called the ampulla (meaning "flask").

Sperm make up only 5 percent of the final volume of **semen**, the thick, milky fluid that the male ejaculates. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

Seminal Vesicles

As sperm pass through the ampulla of the vas deferens at ejaculation, they mix with fluid from the associated **seminal vesicle** (see [link]). The paired seminal vesicles are glands that contribute approximately 60 percent of the semen volume. Seminal vesicle fluid is alkaline in order to neutralize acids in the vagina. The fluid contains the following substances: 1) large amounts of fructose, which is used by the sperm mitochondria to generate ATP to allow movement through the female reproductive tract, 2) enzymes to

facilitate semen clotting after ejaculation in efforts to retain the semen in the female reproductive tract, and 3) prostaglandins to contribute to motility and viability of sperm.

The fluid, now containing both sperm and seminal vesicle secretions, next moves into the associated **ejaculatory duct**, a short structure formed from the ampulla of the vas deferens and the duct of the seminal vesicle. The paired ejaculatory ducts transport the seminal fluid into the next structure, the prostate gland.

Prostate Gland

As shown in [link], the centrally located **prostate gland** sits anterior to the rectum at the base of the bladder surrounding the urethra. About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid, now called semen. This fluid contains: 1)citrate, zinc, and acid phosphatase; their function is unknown, and 2)enzymes to degrade clotted semen after entry into the female reproductive tract so sperm can pass farther into the female reproductive tract.

The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again. This enlargement does not usually cause problems; however, abnormal growth of the prostate, or benign prostatic hyperplasia (BPH), can cause constriction of the urethra as it passes through the middle of the prostate gland, leading to a number of lower urinary tract symptoms, such as a frequent and intense urge to urinate, a weak stream, and a sensation that the bladder has not emptied completely. By age 60, approximately 40 percent of men have some degree of BPH. By age 80, the number of affected individuals has jumped to as many as 80 percent. Treatments for BPH attempt to relieve the pressure on the urethra so that urine can flow more normally. Mild to moderate symptoms are treated with medication, whereas severe enlargement of the prostate is treated by surgery in which a portion of the prostate tissue is removed.

Another common disorder involving the prostate is prostate cancer. According to the Centers for Disease Control and Prevention (CDC), prostate cancer is the second most common cancer in men. However, some forms of prostate cancer grow very slowly and thus may not ever require treatment. Aggressive forms of prostate cancer, in contrast, involve metastasis to vulnerable organs like the lungs and brain. There is no link between BPH and prostate cancer, but the symptoms are similar. Prostate cancer is detected by a medical history, a blood test, and a rectal exam that allows physicians to palpate the prostate and check for unusual masses. If a mass is detected, the cancer diagnosis is confirmed by biopsy of the cells.

Bulbourethral Glands

The final addition to semen is made by two **bulbourethral glands** (or Cowper's glands) that release a thick, salty fluid that lubricates the end of the urethra and the vagina, and helps to clean urine residues from the penile urethra. The fluid from these accessory glands is released after the male becomes sexually aroused, and shortly before the release of the semen. It is therefore sometimes called pre-ejaculate. It is important to note that, in addition to the lubricating proteins, it is possible for bulbourethral fluid to pick up sperm already present in the urethra, and therefore it may be able to cause pregnancy.

Note:

Interactive Link Feature



Watch this <u>video</u> to explore the structures of the male reproductive system and the path of sperm, which starts in the testes and ends as the sperm leave the penis through the urethra. Where are sperm deposited after they leave the ejaculatory duct?

The Penis

The **penis** is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen into the female reproductive tract.

Both sexual arousal and REM sleep (during which dreaming occurs) can induce an erection. Penile erections are controlled by the autonomic nervous system and are spinal reflexes. There are three phases in this sexual response: erection, emission, and ejaculation. During sexual arousal, parasympathetic activity to neurons in the penis is increased. This innervation causes nitric oxide (NO) to be released from nerve endings near blood vessels within the penis. Release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis and induces the endothelial cells in the penile arterial walls to also secrete NO and perpetuate the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. The result of this increased blood flow to the penis and reduced blood return from the penis is erection. Depending on the flaccid dimensions of a penis, it can increase in size slightly or greatly during erection, with the average length of an erect penis measuring approximately 15 cm. The emission phase occurs next. During this phase, the neural activity shifts from parasympathetic to sympathetic control. Sympathetic innervation causes the contraction of the epididymis, vas deferens, and ejaculatory ducts. The secretions from each of these structures will then aid in the movement of the semen into the urethra. This phase is followed by the ejaculation phase. Sexual arousal continues as does the sympathetic response. This response causes contraction of the smooth muscle in the urethra skeletal muscle at the base of the penis, and contraction (closure) of the urethral sphincter. The result is movement of semen from the urethra to the outside of the body.

Note:

Disorders of the... Feature Male Reproductive System

Erectile dysfunction (ED) is a condition in which a man has difficulty either initiating or maintaining an erection. The combined prevalence of minimal, moderate, and complete ED is approximately 40 percent in men at age 40, and reaches nearly 70 percent by 70 years of age. In addition to aging, ED is associated with diabetes, vascular disease, psychiatric disorders, prostate disorders, the use of some drugs such as certain antidepressants, and problems with the testes resulting in low testosterone concentrations. These physical and emotional conditions can lead to interruptions in the vasodilation pathway and result in an inability to achieve an erection.

Recall that the release of NO induces relaxation of the smooth muscles that surround the penile arteries, leading to the vasodilation necessary to achieve an erection. To reverse the process of vasodilation, an enzyme called phosphodiesterase (PDE) degrades a key component of the NO signaling pathway called cGMP. There are several different forms of this enzyme, and PDE type 5 is the type of PDE found in the tissues of the penis. Scientists discovered that inhibiting PDE5 increases blood flow, and allows vasodilation of the penis to occur.

PDEs and the vasodilation signaling pathway are found in the vasculature in other parts of the body. In the 1990s, clinical trials of a PDE5 inhibitor called sildenafil were initiated to treat hypertension and angina pectoris (chest pain caused by poor blood flow through the heart). The trial showed that the drug was not effective at treating heart conditions, but many men experienced erection and priapism (erection lasting longer than 4 hours). Because of this, a clinical trial was started to investigate the ability of sildenafil to promote erections in men suffering from ED. In 1998, the FDA approved the drug, marketed as Viagra[®]. Since approval of the drug,

sildenafil and similar PDE inhibitors now generate over a billion dollars a year in sales, and are reported to be effective in treating approximately 70 to 85 percent of cases of ED. Importantly, men with health problems—especially those with cardiac disease taking nitrates—should avoid Viagra or talk to their physician to find out if they are a candidate for the use of this drug, as deaths have been reported for at-risk users.

Testosterone

Testosterone, an androgen, is a steroid hormone produced by **Leydig cells**. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical differentiation of the male sexual organs. In childhood, testosterone concentrations are low. They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

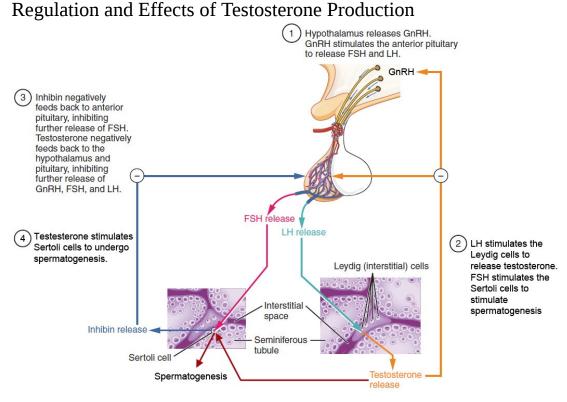
Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and Leydig cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intratesticular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development via protein synthesis, bone growth, development and growth of accessory reproductive organs, the development of secondary sex characteristics, and maintaining libido (sex drive) in both males and females. In females, the ovaries secrete small amounts of testosterone,

although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both sexes.

Control of Testosterone

The regulation of testosterone concentrations throughout the body is critical for male reproductive function. The intricate interplay between the endocrine system and the reproductive system is shown in [link].



The hypothalamus and pituitary gland regulate the production of testosterone and the cells that assist in spermatogenesis. GnRH activates the anterior pituitary to produce LH and FSH, which in turn stimulate Leydig cells and Sertoli cells, respectively. The system is a negative feedback loop because the end products of the pathway, testosterone and inhibin, interact with the activity of GnRH to inhibit their own production.

The regulation of Leydig cell production of testosterone begins outside of the testes. The hypothalamus and the pituitary gland in the brain integrate external and internal signals to control testosterone synthesis and secretion. The regulation begins in the hypothalamus. Pulsatile release of a hormone called **gonadotropin-releasing hormone (GnRH)** from the hypothalamus stimulates the endocrine release of hormones from the pituitary gland. Binding of GnRH to its receptors on the anterior pituitary gland stimulates release of the two gonadotropins: luteinizing hormone (LH) and folliclestimulating hormone (FSH). These two hormones are critical for reproductive function in both men and women. In men, FSH binds predominantly to the Sertoli cells within the seminiferous tubules to promote spermatogenesis. FSH also stimulates the Sertoli cells to produce hormones called inhibins, which function to inhibit FSH release from the pituitary, thus reducing testosterone secretion. These polypeptide hormones correlate directly with Sertoli cell function and sperm number; inhibin B can be used as a marker of spermatogenic activity. In men, LH binds to receptors on Leydig cells in the testes and upregulates the production of testosterone.

A negative feedback loop predominantly controls the synthesis and secretion of both FSH and LH. Low blood concentrations of testosterone stimulate the hypothalamic release of GnRH. GnRH then stimulates the anterior pituitary to secrete LH into the bloodstream. In the testis, LH binds to LH receptors on Leydig cells and stimulates the release of testosterone. When concentrations of testosterone in the blood reach a critical threshold, testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.

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Aging and the... Feature Male Reproductive System

Declines in Leydig cell activity can occur in men beginning at 40 to 50 years of age. The resulting reduction in circulating testosterone concentrations can lead to symptoms of andropause, also known as male menopause. While the reduction in sex steroids in men is akin to female menopause, there is no clear sign—such as a lack of a menstrual period—to denote the initiation of andropause. Instead, men report feelings of fatigue, reduced muscle mass, depression, anxiety, irritability, loss of libido, and insomnia. A reduction in spermatogenesis resulting in lowered fertility is also reported, and sexual dysfunction can also be associated with andropausal symptoms.

Whereas some researchers believe that certain aspects of andropause are difficult to tease apart from aging in general, testosterone replacement is sometimes prescribed to alleviate some symptoms. Recent studies have shown a benefit from androgen replacement therapy on the new onset of depression in elderly men; however, other studies caution against testosterone replacement for long-term treatment of andropause symptoms, showing that high doses can sharply increase the risk of both heart disease and prostate cancer.

Chapter Review

Gametes are the reproductive cells that combine to form offspring. Organs called gonads produce the gametes, along with the hormones that regulate human reproduction. The male gametes are called sperm. Spermatogenesis, the production of sperm, occurs within the seminiferous tubules that make up most of the testis. The scrotum is the muscular sac that holds the testes outside of the body cavity.

Spermatogenesis begins with mitotic division of spermatogonia (stem cells) to produce primary spermatocytes that undergo the two divisions of meiosis to become secondary spermatocytes, then the haploid spermatids. During spermiogenesis, spermatids are transformed into spermatozoa (formed sperm). Upon release from the seminiferous tubules, sperm are moved to

the epididymis where they continue to mature. During ejaculation, sperm exit the epididymis through the vans (ductus) deferens, a duct in the spermatic cord that leaves the scrotum. The ampulla of the vans deferens meets the seminal vesicle, a gland that contributes fructose and proteins, at the ejaculatory duct. The fluid continues through the urethra, where secretions from the prostate are added to form semen. These secretions help the sperm to travel through the urethra and into the female reproductive tract. Secretions from the bulbourethral glands protect sperm and cleanse and lubricate the penile urethra.

The penis is the male organ of copulation. Columns of erectile tissue fill with blood when sexual arousal activates vasodilatation in the blood vessels of the penis. Testosterone regulates and maintains the sex organs and sex drive, and induces the physical changes of puberty. Interplay between the testes and the endocrine system precisely control the production of testosterone with a negative feedback loop.

Glossary

blood-testis barrier

tight junctions between Sertoli cells that prevent bloodborne pathogens from gaining access to later stages of spermatogenesis and prevent the potential for an autoimmune reaction to haploid sperm

bulbourethral glands

(also, Cowper's glands) glands that secrete a lubricating mucus that cleans and lubricates the urethra prior to and during ejaculation

ejaculatory duct

duct that connects the ampulla of the ductus deferens with the duct of the seminal vesicle at the prostatic urethra

epididymis

(plural = epididymides) coiled tubular structure in which sperm start to mature and are stored until ejaculation

gamete

haploid reproductive cell that contributes genetic material to form an offspring

gonadotropin-releasing hormone (GnRH)

hormone released by the hypothalamus that regulates the production of follicle-stimulating hormone and luteinizing hormone from the pituitary gland

gonads

reproductive organs (testes in men and ovaries in women) that produce gametes and reproductive hormones

Leydig cells

cells between the seminiferous tubules of the testes that produce testosterone; a type of interstitial cell

penis

male organ of copulation

prostate gland

doughnut-shaped gland at the base of the bladder surrounding the urethra and contributing fluid to semen during ejaculation

scrotum

external pouch of skin and muscle that houses the testes

semen

ejaculatory fluid composed of sperm and secretions from the seminal vesicles, prostate, and bulbourethral glands

seminal vesicle

gland that produces seminal fluid, which contributes to semen

seminiferous tubules

tube structures within the testes where spermatogenesis occurs

Sertoli cells

cells that support germ cells through the process of spermatogenesis; a type of sustentacular cell

sperm

(also, spermatozoon) male gamete

spermatid

immature sperm cells produced by meiosis II of secondary spermatocytes

spermatocyte

cell that results from the division of spermatogonium and undergoes meiosis I and meiosis II to form spermatids

spermatogenesis

formation of new sperm, occurs in the seminiferous tubules of the testes

spermatogonia

(singular = spermatogonium) diploid precursor cells that become sperm

spermiogenesis

transformation of spermatids to spermatozoa during spermatogenesis

testes

(singular = testis) male gonads

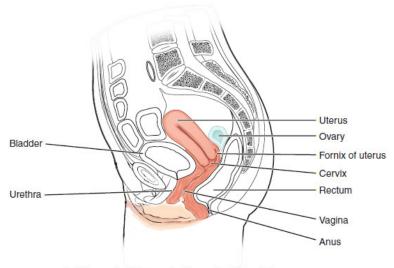
vas deferens

(also, ductus deferens) duct that transports sperm from the epididymis through the spermatic cord and into the ejaculatory duct; also referred as the ductus deferens OU Human Physiology: Anatomy and Physiology of the Female Reproductive System

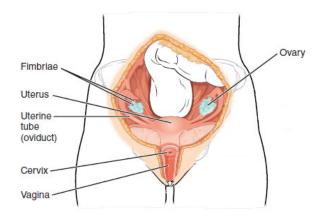
By the end of this section, you will be able to:

- Describe the structure and function of the major and accessory organs of the female reproductive system
- Explain the events in oogenesis through fertilization
- Describe the events of the ovarian cycle including follicle development, ova development, and hormone involvement
- Describe the hormonal changes that occur during the mid-follicular, late follicular, and luteal phases of the ovarian cycle and uterine cycle
- Describe the events of the uterine cycle including the menstrual, proliferative, and secretory phases, as well as hormone involvement
- Describe how aging affects female reproduction

The female reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity ([link]). Recall that the ovaries are the female gonads. The gamete they produce is called an **oocyte**. We'll discuss the production of oocytes in detail shortly. First, let's look at some of the structures of the female reproductive system. Female Reproductive System



(a) Human female reproductive system: lateral view



(b) Human female reproductive system: anterior view

The major organs of the female reproductive system are located inside the pelvic cavity.

Vagina

The **vagina**, shown at the bottom of [link], is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract and is therefore referred to as the female organ of copulation. It also serves as the exit from the uterus during menses and childbirth. The walls

of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called rugae. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy woman, the most predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (below 4.5). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ. However, douching—or washing out the vagina with fluid—can disrupt the normal balance of healthy microorganisms, and actually increase a woman's risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that women do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora.

Ovaries

The **ovaries** are the female gonads (see [link]). Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovary comprises an outer covering of cuboidal epithelium that is superficial to a dense connective tissue covering. Beneath this covering is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework that forms the bulk of the adult ovary. Oocytes develop within this outer layer, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a **follicle**. The growth and development of ovarian follicles will be described shortly.

The Ovarian Cycle

The **ovarian cycle** is a set of predictable changes in a female's oocytes and ovarian follicles. During a woman's reproductive years, it is a roughly 28-

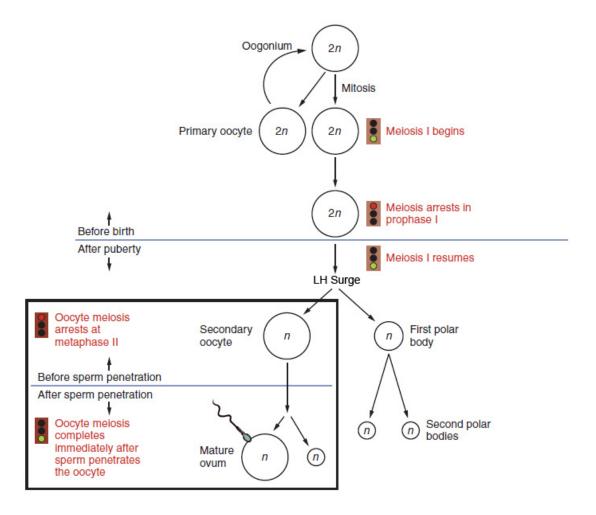
day cycle that can be correlated with, but is not the same as, the uterine cycle (discussed shortly). The ovarian cycle is divided into two phases, the follicular phase and the luteal phase. The follicular phase lasts from day 1 (menstruation) to day 14 (ovulation) and the luteal phase lasts from day 14 (ovulation) to day 28. These phases include two interrelated processes: oogenesis (the production of female gametes) and folliculogenesis (the growth and development of ovarian follicles). These two processes are occurring simultaneously.

Oogenesis

Gametogenesis in females is called **oogenesis**. The process begins with the ovarian stem cells, or **oogonia** ([link]). Oogonia are formed during fetal development, and divide via mitosis, much like spermatogonia in the testis. Unlike spermatogonia, however, oogonia form primary oocytes in the fetal ovary prior to birth. These primary oocytes are then arrested in this stage of meiosis I, only to resume it years later, beginning at puberty and continuing until the woman is near menopause (the cessation of a woman's reproductive functions). The number of primary oocytes present in the ovaries declines from one to two million in an infant, to approximately 400,000 at puberty, to zero by the end of menopause.

The initiation of **ovulation**—the release of an oocyte from the ovary—marks the transition from puberty into reproductive maturity for women. From then on, throughout a woman's reproductive years, ovulation occurs approximately once every 28 days. Just prior to ovulation, a surge of luteinizing hormone triggers the resumption of meiosis in a primary oocyte. This initiates the transition from primary to secondary oocyte. However, as you can see in [link], this cell division does not result in two identical cells. Instead, the cytoplasm is divided unequally, and one daughter cell is much larger than the other. This larger cell, the secondary oocyte, eventually leaves the ovary during ovulation. The smaller cell, called the first **polar body**, may or may not complete meiosis and produce second polar bodies; in either case, it eventually disintegrates. Therefore, even though oogenesis produces up to four cells, only one survives.

Oogenesis



The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if there is penetration of the secondary oocyte by a sperm cell.

How does the diploid secondary oocyte become an **ovum**—the haploid female gamete? Meiosis of a secondary oocyte is completed only if a sperm succeeds in penetrating its barriers. Meiosis II then resumes, producing one haploid ovum that, at the instant of fertilization by a (haploid) sperm, becomes the first diploid cell of the new offspring (a zygote). Thus, the ovum can be thought of as a brief, transitional, haploid stage between the diploid oocyte and diploid zygote.

The larger amount of cytoplasm contained in the female gamete is used to supply the developing zygote with nutrients during the period between fertilization and implantation into the uterus. Interestingly, sperm contribute only DNA at fertilization —not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of maternal origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was maternally inherited, meaning that you can trace your mitochondrial DNA directly to your mother, her mother, and so on back through your female ancestors.

Note:

Everyday Connections Feature

Mapping Human History with Mitochondrial DNA

When we talk about human DNA, we're usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from our father, and half from our mother. However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the fat ovum we inherit from our mother. She received her mtDNA from her mother, who got it from her mother, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.

Mutations (changes) in mtDNA occur spontaneously in a somewhat organized pattern at regular intervals in human history. By analyzing these mutational relationships, researchers have been able to determine that we can all trace our ancestry back to one woman who lived in Africa about 200,000 years ago. Scientists have given this woman the biblical name Eve, although she is not, of course, the first *Homo sapiens* female. More precisely, she is our most recent common ancestor through matrilineal descent.

This doesn't mean that everyone's mtDNA today looks exactly like that of our ancestral Eve. Because of the spontaneous mutations in mtDNA that have occurred over the centuries, researchers can map different "branches" off of the "main trunk" of our mtDNA family tree. Your mtDNA might

have a pattern of mutations that aligns more closely with one branch, and your neighbor's may align with another branch. Still, all branches eventually lead back to Eve.

But what happened to the mtDNA of all of the other *Homo sapiens* females who were living at the time of Eve? Researchers explain that, over the centuries, their female descendants died childless or with only male children, and thus, their maternal line—and its mtDNA—ended.

Folliculogenesis

Again, ovarian follicles are oocytes and their supporting cells. They grow and develop in a process called **folliculogenesis**, which typically leads to ovulation of one follicle approximately every 28 days, along with death to multiple other follicles. The death of ovarian follicles is called atresia, and can occur at any point during follicular development. Recall that, a female infant at birth will have one to two million oocytes within her ovarian follicles, and that this number declines throughout life until menopause, when no follicles remain. As you'll see next, follicles progress from primordial, to primary, to secondary and tertiary stages prior to ovulation—with the oocyte inside the follicle remaining as a primary oocyte until right before ovulation.

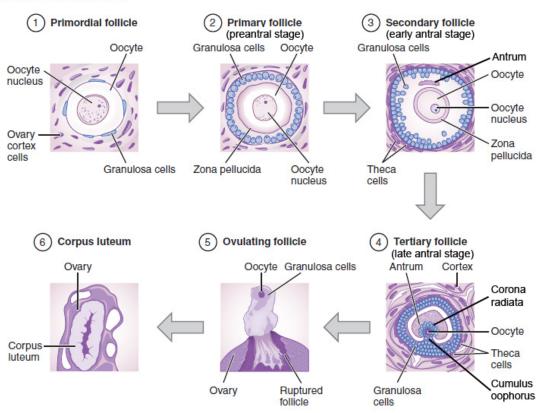
Folliculogenesis begins with follicles in a resting state. These small **primordial follicles** are present in newborn females and are the prevailing follicle type in the adult ovary ([link]). Primordial follicles have only a single flat layer of support cells, called **granulosa cells**, that surround the oocyte, and they can stay in this resting state for years—some until right before menopause.

After puberty, a few primordial follicles will respond to a recruitment signal each day, and will join a pool of immature growing follicles called **primary follicles**. Primary follicles start with a single layer of granulosa cells, but the granulosa cells then become active and transition from a flat or squamous shape to a rounded, cuboidal shape as they increase in size and proliferate. As the granulosa cells divide, the follicles—now called **secondary follicles** (see [link])—increase in diameter, adding a new outer

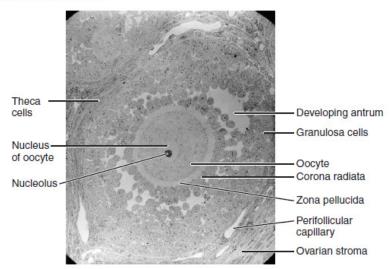
layer of connective tissue, blood vessels, and **theca cells**—cells that work with the granulosa cells to produce estrogens.

Within the growing secondary follicle, the primary oocyte now secretes a thin acellular membrane called the zona pellucida that will play a critical role in fertilization. A thick fluid, called follicular fluid, that has formed between the granulosa cells also begins to collect into one large pool, or **antrum**. Follicles in which the antrum has become large and fully formed are considered **tertiary follicles** (or late antral follicles). Several follicles reach the tertiary stage at the same time, and most of these will undergo atresia. The one that does not die will continue to grow and develop until ovulation, when it will expel its secondary oocyte surrounded by several layers of granulosa cells from the ovary. Keep in mind that most follicles don't make it to this point. In fact, roughly 99 percent of the follicles in the ovary will undergo atresia, which can occur at any stage of folliculogenesis. Folliculogenesis

(a) Stages of Folliculogenesis



(b) A Secondary Follicle



(a) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates the production of estrogen by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells

remaining in the follicle then develop into the corpus luteum.

(b) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are clearly visible. EM × 1100. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Hormonal Control of the Ovarian Cycle

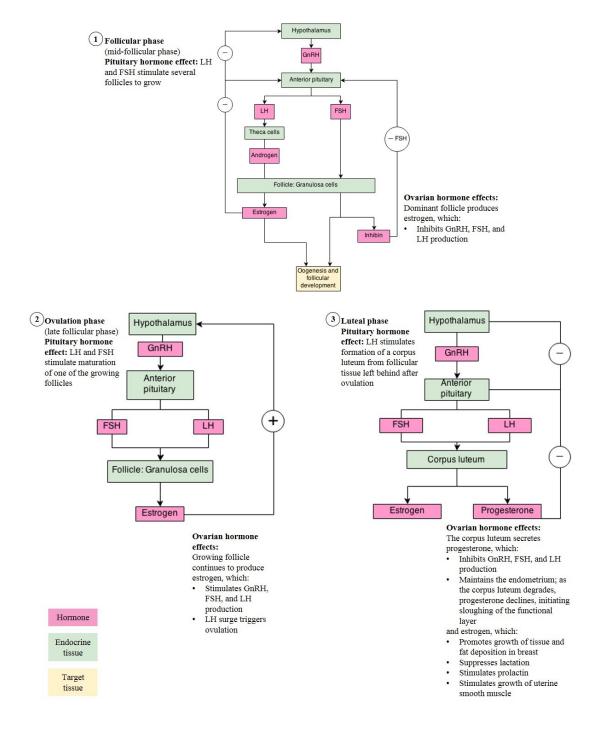
The process of development that we have just described, from primordial follicle to early tertiary follicle, takes approximately two months in humans. The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. These changes are regulated by many of the same hormones that regulate the male reproductive system, including GnRH, LH, and FSH.

As in men, the hypothalamus produces GnRH, a hormone that signals the anterior pituitary gland to produce the gonadotropins FSH and LH ([link]). These gonadotropins leave the pituitary and travel through the bloodstream to the ovaries, where they bind to receptors on the granulosa and theca cells of the follicles. FSH binds to granulose cells and stimulates oogenesis and the follicles to grow (hence its name of follicle-stimulating hormone), and the five or six tertiary follicles expand in diameter. The release of LH also stimulates the granulosa and theca cells of the follicles. Upon stimulation, the theca cells will produce the sex steroid hormone estradiol, a type of estrogen, that will ultimately be enzymatically converted to estrogen via the granulosa cells. Estrogen will then stimulate oogenesis and follicular development by the granulosa cells and plasma estrogen levels will increase. This phase of the ovarian cycle, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase.

The more granulosa and theca cells a follicle has (that is, the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of

estrogen, systemic plasma estrogen concentrations increase. Following a classic negative feedback loop, the high concentrations of estrogen will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Inhibin, like in the male testes, will also stop synthesis and secretion of FSH from the anterior pituitary. Because the large tertiary follicles require FSH to grow and survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia). Typically only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte. Scientists have studied many factors that lead to a particular follicle becoming dominant: size, the number of granulosa cells, and the number of FSH receptors on those granulosa cells all contribute to a follicle becoming the one surviving dominant follicle.

Hormonal Regulation of Ovulation



The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the production of estrogen and progesterone by the ovaries.

When only the one dominant follicle remains in the ovary, the granulosa cells again begin to secrete estrogen. It produces more estrogen than all of the developing follicles did together before the negative feedback occurred. It produces so much estrogen that the normal negative feedback does not occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream (see [link]). The positive feedback loop by which more estrogen triggers release of more LH and FSH only occurs at this point in the cycle.

It is this large burst of LH (called the LH surge) that leads to ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle, including stimulating the resumption of meiosis of the primary oocyte to a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge will also cause the granulosa cells to secrete a small amount of progesterone and triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release is ovulation.

In the next section, you will follow the ovulated oocyte as it travels toward the uterus, but there is one more important event that occurs in the ovarian cycle. The surge of LH also stimulates a change in the granulosa and theca cells that remain in the follicle after the oocyte has been ovulated. This change is called luteinization (recall that the full name of LH is luteinizing hormone), and it transforms the collapsed follicle (the granulosa and theca cells) into a new endocrine structure called the **corpus luteum**, a term meaning "yellowish body" (see [link]). The luteinized granulosa and theca cells of the corpus luteum begin to produce large amounts of the sex steroid hormone progesterone, a hormone that is critical for the establishment and maintenance of pregnancy and a moderate amount of estrogen. Progesterone triggers negative feedback at the hypothalamus and pituitary, which keeps GnRH, LH, and FSH secretions low, so no new dominant follicles develop at this time.

The post-ovulatory phase of progesterone secretion is known as the luteal phase of the ovarian cycle. If pregnancy does not occur within 10 to 12 days, the corpus luteum will stop secreting progesterone and degrade into the **corpus albicans**, a nonfunctional "whitish body" that will disintegrate in the ovary over a period of several months. During this time of reduced progesterone secretion, FSH and LH are once again stimulated, and the follicular phase begins again with a new cohort of early tertiary follicles beginning to grow and secrete estrogen.

The Uterine Tubes

The **uterine tubes** (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus ([link]). Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections. The isthmus is the narrow end of each uterine tube that is connected to the uterus. The wide distal **infundibulum** flares out with slender, finger-like projections called **fimbriae**. The middle region of the tube, called the **ampulla**, is where fertilization often occurs.

Following ovulation, the secondary oocyte surrounded by a few granulosa cells is released into the peritoneal cavity. The nearby uterine tube, either left or right, receives the oocyte. Unlike sperm, oocytes lack flagella, and therefore cannot move on their own. So how do they travel into the uterine tube and toward the uterus? High concentrations of estrogen that occur around the time of ovulation induce contractions of the smooth muscle along the length of the uterine tube. These contractions occur every 4 to 8 seconds, and the result is a coordinated movement that sweeps the surface of the ovary and the pelvic cavity. Current flowing toward the uterus is generated by coordinated beating of the cilia that line the outside and lumen of the length of the uterine tube. These cilia beat more strongly in response to the high estrogen concentrations that occur around the time of ovulation. As a result of these mechanisms, the oocyte–granulosa cell complex is pulled into the interior of the tube. Once inside, the muscular contractions and beating cilia move the oocyte slowly toward the uterus. When fertilization does occur, sperm typically meet the egg while it is still moving through the uterine tubes.

Note:

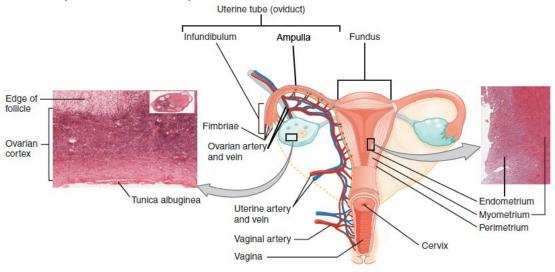
Interactive Link



Watch this <u>video</u> to observe ovulation and its initiation in response to the release of FSH and LH from the pituitary gland. What specialized structures help guide the oocyte from the ovary into the uterine tube?

If the oocyte is successfully fertilized, the resulting zygote will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow. If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.

Ovaries, Uterine Tubes, and Uterus



This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the

distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The open-ended structure of the uterine tubes can have significant health consequences if bacteria or other contagions enter through the vagina and move through the uterus, into the tubes, and then into the pelvic cavity. If this is left unchecked, a bacterial infection (sepsis) could quickly become life-threatening. The spread of an infection in this manner is of special concern when unskilled practitioners perform abortions in non-sterile conditions. Sepsis is also associated with sexually transmitted bacterial infections, especially gonorrhea and chlamydia. These increase a woman's risk for pelvic inflammatory disease (PID), infection of the uterine tubes or other reproductive organs. Even when resolved, PID can leave scar tissue in the tubes, leading to infertility.

Note:

Interactive Link



Watch this series of <u>videos</u> to look at the movement of the oocyte through the ovary. The cilia in the uterine tube promote movement of the oocyte. What would likely occur if the cilia were paralyzed at the time of ovulation?

The Uterus and Cervix

The **uterus** is the muscular organ that nourishes and supports the growing embryo (see [link]). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the **fundus**. The middle section of the uterus is called the **body of uterus** (or corpus). The **cervix** is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

The wall of the uterus is made up of three layers. The most superficial layer is the serous membrane, or **perimetrium**, which consists of epithelial tissue that covers the exterior portion of the uterus. The middle layer, or **myometrium**, is a thick layer of smooth muscle responsible for uterine contractions. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman's period. Anteriorly directed myometrial contractions also occur near the time of ovulation, and are thought to possibly facilitate the transport of sperm through the female reproductive tract.

The innermost layer of the uterus is called the **endometrium**. The endometrium contains a connective tissue lining, the lamina propria, which is covered by epithelial tissue that lines the lumen. Structurally, the endometrium consists of two layers: the stratum basalis and the stratum functionalis (the basal and functional layers). The basal layer is part of the lamina propria and is adjacent to the myometrium; this layer does not shed during menses. In contrast, the thicker functional layer contains the glandular portion of the lamina propria and the endothelial tissue that lines the uterine lumen. It is the functional layer that grows and thickens in response to increased levels of estrogen and progesterone. In the luteal phase of the menstrual cycle, special branches off of the uterine artery called spiral arteries supply the thickened functional layer. This inner functional layer provides the proper site of implantation for the fertilized

egg, and—should fertilization not occur—it is only this layer of the endometrium that sheds during menstruation.

Recall that during the follicular phase of the ovarian cycle, the tertiary follicles are growing and secreting estrogen. At the same time, the functional layer of the endometrium is thickening to prepare for a potential implantation. The post-ovulatory increase in progesterone, which characterizes the luteal phase, is key for maintaining a thick functional layer. As long as a functional corpus luteum is present in the ovary, the endometrial lining is prepared for implantation. Indeed, if an embryo implants, signals are sent to the corpus luteum to continue secreting progesterone to maintain the endometrium, and thus maintain the pregnancy. If an embryo does not implant, no signal is sent to the corpus luteum and it degrades, ceasing progesterone production and ending the luteal phase. Without progesterone, the endometrium thins and, under the influence of prostaglandins, the spiral arteries of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a result, endometrial tissue dies and blood, pieces of the endometrial tissue, and white blood cells are shed through the vagina during menstruation, or the **menses**. The first menses after puberty, called **menarche**, can occur either before or after the first ovulation.

The Uterine Cycle

Now that we have discussed the maturation of the cohort of tertiary follicles in the ovary, the build-up and then shedding of the endometrial lining in the uterus, and the function of the uterine tubes and vagina, we can put everything together to talk about the three phases of the **uterine cycle**—the series of changes in which the uterine lining is shed, rebuilds, and prepares for implantation.

The timing of the uterine cycle starts with the first day of menses, referred to as day one of a woman's period. Cycle length is determined by counting the days between the onset of bleeding in two subsequent cycles. Because the average length of a woman's uterine cycle is 28 days, this is the time period used to identify the timing of events in the cycle. However, the

length of the uterine cycle varies among women, and even in the same woman from one cycle to the next, typically from 21 to 32 days.

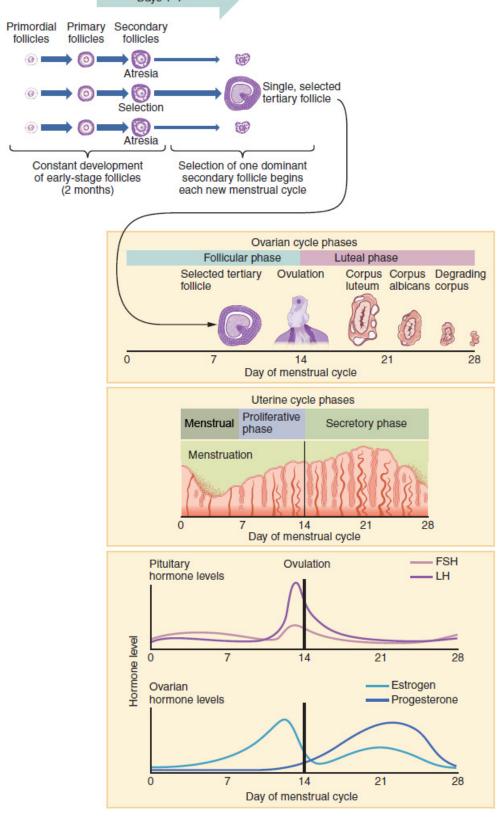
Just as the hormones produced by the granulosa and theca cells of the ovary "drive" the follicular and luteal phases of the ovarian cycle, they also control the three distinct phases of the uterine cycle. These are the menstrual phase, the proliferative phase, and the secretory phase.

Menstrual Phase

The **menstrual phase** of the uterine cycle is the phase during which the lining is shed; that is, the days that the woman menstruates. Although it averages approximately five days (day 1-5), the menstrual phase can last from 2 to 7 days, or longer. As shown in [link], the menstrual phase occurs during the early days of the follicular phase of the ovarian cycle, when progesterone, FSH, and LH levels are low. Recall that progesterone concentrations decline as a result of the degradation of the corpus luteum, marking the end of the luteal phase. This decline in progesterone triggers the shedding of the functional layer of the endometrium.

Hormone Levels in Ovarian and Uterine Cycles

Follicular phase Days 1–7



The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and uterine cycles. The uterine cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge.

Proliferative Phase

Once menstrual flow ceases, the endometrium begins to proliferate again, marking the beginning of the **proliferative phase** of the uterine cycle (see [link]). It occurs when the granulosa and theca cells of the tertiary follicles begin to produce increased amounts of estrogen. These rising estrogen concentrations stimulate the endometrial lining to rebuild.

Recall that the high estrogen concentrations will eventually lead to a decrease in FSH as a result of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback —which occurs with the elevated estrogen production from the dominant follicle—then stimulates the LH surge that will trigger ovulation. In a typical 28-day uterine cycle, ovulation occurs on day 14. Ovulation marks the end of the proliferative phase as well as the end of the follicular phase.

Secretory Phase

In addition to prompting the LH surge, high estrogen levels increase the uterine tube contractions that facilitate the pick-up and transfer of the ovulated oocyte. High estrogen levels also slightly decrease the acidity of the vagina, making it more hospitable to sperm. In the ovary, the luteinization of the granulosa cells of the collapsed follicle forms the progesterone-producing corpus luteum, marking the beginning of the luteal

phase of the ovarian cycle. In the uterus, progesterone from the corpus luteum begins the **secretory phase** of the uterine cycle, in which the endometrial lining prepares for implantation (see [link]). Over the next 10 to 12 days, the endometrial glands secrete a fluid rich in glycogen. If fertilization has occurred, this fluid will nourish the ball of cells now developing from the zygote. At the same time, the spiral arteries develop to provide blood to the thickened functional layer of the endometrium.

If no pregnancy occurs within approximately 10 to 12 days, the corpus luteum will degrade into the corpus albicans. Levels of both estrogen and progesterone will fall, and the endometrium will grow thinner. Prostaglandins will be secreted that cause constriction of the spiral arteries, reducing oxygen supply. The endometrial tissue will die, resulting in menses—or the first day of the next cycle.

Note:

Disorders of the... Feature **Female Reproductive System**

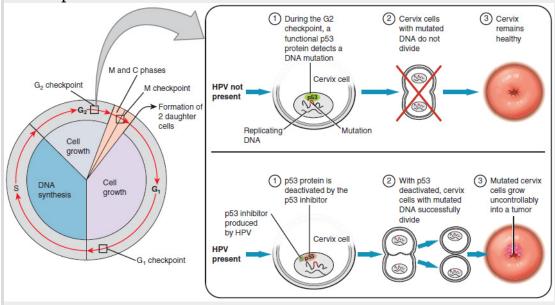
Research over many years has confirmed that cervical cancer is most often caused by a sexually transmitted infection with human papillomavirus (HPV). There are over 100 related viruses in the HPV family, and the characteristics of each strain determine the outcome of the infection. In all cases, the virus enters body cells and uses its own genetic material to take over the host cell's metabolic machinery and produce more virus particles. HPV infections are common in both men and women. Indeed, a recent study determined that 42.5 percent of females had HPV at the time of testing. These women ranged in age from 14 to 59 years and differed in race, ethnicity, and number of sexual partners. Of note, the prevalence of HPV infection was 53.8 percent among women aged 20 to 24 years, the age group with the highest infection rate.

HPV strains are classified as high or low risk according to their potential to cause cancer. Though most HPV infections do not cause disease, the disruption of normal cellular functions in the low-risk forms of HPV can cause the male or female human host to develop genital warts. Often, the body is able to clear an HPV infection by normal immune responses within

2 years. However, the more serious, high-risk infection by certain types of HPV can result in cancer of the cervix ([link]). Infection with either of the cancer-causing variants HPV 16 or HPV 18 has been linked to more than 70 percent of all cervical cancer diagnoses. Although even these high-risk HPV strains can be cleared from the body over time, infections persist in some individuals. If this happens, the HPV infection can influence the cells of the cervix to develop precancerous changes.

Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.

Development of Cervical Cancer



In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.

When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is p53. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the cell cycle—allowing time for DNA repair to occur—or initiates apoptosis.

Both of these processes prevent the accumulation of mutations in a cell's genome. High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. Pap smears sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, women in developing countries often do not have access to regular pap smears. As a result, these women account for as many as 80 percent of the cases of cervical cancer worldwide.

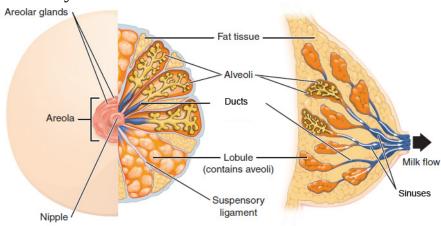
In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for women, because HPV is sexually transmitted, both men and women require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many women worldwide.

The Breasts

Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented **areola** ([link]), whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast milk is produced by the **mammary glands**, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 ducts that open on the surface of the nipple. These ducts each extend to a sinus that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called **alveoli** (see [link]). The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the sinuses. From here, the baby can draw milk through the ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced.

Anatomy of the Breast



During lactation, milk moves from the alveoli through the lactiferous ducts to the nipple.

During the normal hormonal fluctuations in the menstrual cycle, breast tissue responds to changing levels of estrogen and progesterone, which can lead to swelling and breast tenderness in some individuals, especially during the secretory phase. If pregnancy occurs, the increase in hormones leads to further development of the mammary tissue and enlargement of the breasts.

Hormonal Birth Control

Birth control pills take advantage of the negative feedback system that regulates the ovarian and menstrual cycles to stop ovulation and prevent pregnancy. Typically they work by providing a constant level of both estrogen and progesterone, which negatively feeds back onto the hypothalamus and pituitary, thus preventing the release of FSH and LH. Without FSH, the follicles do not mature, and without the LH surge, ovulation does not occur. Although the estrogen in birth control pills does stimulate some thickening of the endometrial wall, it is reduced compared with a normal cycle and is less likely to support implantation.

Some birth control pills contain 21 active pills containing hormones, and 7 inactive pills (placebos). The decline in hormones during the week that the woman takes the placebo pills triggers menses, although it is typically lighter than a normal menstrual flow because of the reduced endometrial thickening. Newer types of birth control pills have been developed that deliver low-dose estrogens and progesterone for the entire cycle (these are meant to be taken 365 days a year), and menses never occurs. While some women prefer to have the proof of a lack of pregnancy that a monthly period provides, menstruation every 28 days is not required for health reasons, and there are no reported adverse effects of not having a menstrual period in an otherwise healthy individual.

Because birth control pills function by providing constant estrogen and progesterone levels and disrupting negative feedback, skipping even just one or two pills at certain points of the cycle (or even being several hours late taking the pill) can lead to an increase in FSH and LH and result in ovulation. It is important, therefore, that the woman follow the directions on the birth control pill package to successfully prevent pregnancy.

Note:

Aging and the... Feature

Female Reproductive System

Female fertility (the ability to conceive) peaks when women are in their twenties, and is slowly reduced until a women reaches 35 years of age. After that time, fertility declines more rapidly, until it ends completely at the end of menopause. Menopause is the cessation of the menstrual cycle

that occurs as a result of the loss of ovarian follicles and the hormones that they produce. A woman is considered to have completed menopause if she has not menstruated in a full year. After that point, she is considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur in a woman's forties, or later in her fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.

As a woman reaches the age of menopause, depletion of the number of viable follicles in the ovaries due to atresia affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone inhibin, which normally participates in a negative feedback loop to the pituitary to control the production of FSH. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is primarily the lack of estrogens that leads to the symptoms of menopause.

The earliest changes occur during the menopausal transition, often referred to as peri-menopause, when a women's cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the corpus luteum is reduced. This decline in progesterone can lead to abnormal growth, or hyperplasia, of the endometrium. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are uterine fibroids, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe.

After menopause, lower amounts of estrogens can lead to other changes. Cardiovascular disease becomes as prevalent in women as in men, possibly because estrogens reduce the amount of cholesterol in the blood vessels.

When estrogen is lacking, many women find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. Osteoporosis is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures.

Hormone therapy (HT), which employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, can alleviate some of the symptoms of menopause. In 2002, the Women's Health Initiative began a study to observe women for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when women first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that women on HT have regular pelvic and breast exams.

Chapter Review

The external female genitalia are collectively called the vulva. The vagina is the pathway into and out of the uterus. The man's penis is inserted into the vagina to deliver sperm, and the baby exits the uterus through the vagina during childbirth.

The ovaries produce oocytes, the female gametes, in a process called oogenesis. As with spermatogenesis, meiosis produces the haploid gamete

(in this case, an ovum); however, it is completed only in an oocyte that has been penetrated by a sperm. In the ovary, an oocyte surrounded by supporting cells is called a follicle. In folliculogenesis, primordial follicles develop into primary, secondary, and tertiary follicles. Early tertiary follicles with their fluid-filled antrum will be stimulated by an increase in FSH, a gonadotropin produced by the anterior pituitary, to grow in the 28day ovarian cycle. Supporting granulosa and theca cells in the growing follicles produce estrogens, until the level of estrogen in the bloodstream is high enough that it triggers negative feedback at the hypothalamus and pituitary. This results in a reduction of FSH and LH, and most tertiary follicles in the ovary undergo atresia (they die). One follicle, usually the one with the most FSH receptors, survives this period and is now called the dominant follicle. The dominant follicle produces more estrogen, triggering positive feedback and the LH surge that will induce ovulation. Following ovulation, the granulosa cells of the empty follicle luteinize and transform into the corpus luteum which secretes vasts amounts of progesterone and some estrogen. The ovulated oocyte with its surrounding granulosa cells is picked up by the infundibulum of the uterine tube, and beating cilia help to transport it through the tube toward the uterus. Fertilization occurs within the uterine tube, and the final stage of meiosis is completed.

The uterus has three regions: the fundus, the body, and the cervix. It has three layers: the outer perimetrium, the muscular myometrium, and the inner endometrium. The endometrium responds to estrogen released by the follicles during the menstrual cycle and grows thicker with an increase in blood vessels in preparation for pregnancy. If the egg is not fertilized, no signal is sent to extend the life of the corpus luteum, and it degrades, stopping progesterone and estrogen production. This decline in progesterone results in the sloughing of the inner portion of the endometrium in a process called menses, or menstruation.

he breasts are accessory sexual organs that are utilized after the birth of a child to produce milk in a process called lactation. Birth control pills provide constant levels of estrogen and progesterone to negatively feedback on the hypothalamus and pituitary, and suppress the release of FSH and LH, which inhibits ovulation and prevents pregnancy.

Glossary

alveoli

(of the breast) milk-secreting cells in the mammary gland

ampulla

(of the uterine tube) middle portion of the uterine tube in which fertilization often occurs

antrum

fluid-filled chamber that characterizes a mature tertiary (antral) follicle

areola

highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling

body of uterus

middle section of the uterus

cervix

elongate inferior end of the uterus where it connects to the vagina

corpus albicans

nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum

corpus luteum

transformed follicle after ovulation that secretes progesterone

endometrium

inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

fimbriae

fingerlike projections on the distal uterine tubes

follicle

ovarian structure of one oocyte and surrounding granulosa (and later theca) cells

folliculogenesis

development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins

fundus

(of the uterus) domed portion of the uterus that is superior to the uterine tubes

granulosa cells

supportive cells in the ovarian follicle that produce estrogen

infundibulum

(of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae

mammary glands

glands inside the breast that secrete milk

menarche

first menstruation in a pubertal female

menses

shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

menses phase

phase of the menstrual cycle in which the endometrial lining is shed

menstrual cycle

approximately 28-day cycle of changes in the uterus consisting of a menses phase, a proliferative phase, and a secretory phase

myometrium

smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

oocyte

cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

oogenesis

process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum

oogonia

ovarian stem cells that undergo mitosis during female fetal development to form primary oocytes

ovarian cycle

approximately 28-day cycle of changes in the ovary consisting of a follicular phase and a luteal phase

ovaries

female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

ovulation

release of a secondary oocyte and associated granulosa cells from an ovary

ovum

haploid female gamete resulting from completion of meiosis II at fertilization

perimetrium

outer epithelial layer of uterine wall

polar body

smaller cell produced during the process of meiosis in oogenesis

primary follicles

ovarian follicles with a primary oocyte and one layer of cuboidal granulosa cells

primordial follicles

least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells

proliferative phase

phase of the menstrual cycle in which the endometrium proliferates

secondary follicles

ovarian follicles with a primary oocyte and multiple layers of granulosa cells

secretory phase

phase of the menstrual cycle in which the endometrium secretes a nutrient-rich fluid in preparation for implantation of an embryo

tertiary follicles

(also, antral follicles) ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum

theca cells

estrogen-producing cells in a maturing ovarian follicle

uterine cycle

approximately 28-day cycle of changes in the uterus consisting of a menses phase, a proliferative phase, and a secretory phase

uterine tubes

(also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

uterus

muscular hollow organ in which a fertilized egg develops into a fetus

vagina

tunnel-like organ that provides access to the uterus for the insertion of semen and from the uterus for the birth of a baby

OU Human Physiology: Development of the Male and Female Reproductive Systems

By the end of this section, you will be able to:

- Discuss sex determination and sex differentiation in the embryo and fetus
- Describe the hormonal changes that bring about puberty, and the secondary sex characteristics of men and women

The development of the reproductive systems begins soon after fertilization of the egg, with primordial gonads beginning to develop approximately one month after conception. Reproductive development continues in utero, but there is little change in the reproductive system between infancy and puberty.

Development of the Sexual Organs in the Embryo and Fetus

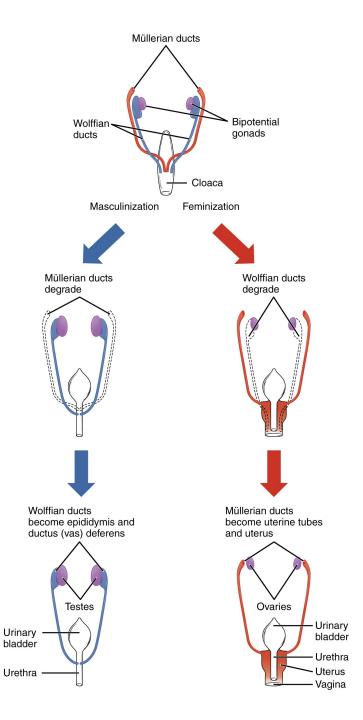
Females are considered the "fundamental" sex—that is, without much chemical prompting, all fertilized eggs would develop into females. To become a male, an individual must be exposed to the cascade of factors initiated by a single gene on the male Y chromosome. This is called the SRY (Sex-determining Region of the Y chromosome). Because females do not have a Y chromosome, they do not have the *SRY* gene. Without a functional *SRY* gene, an individual will be female.

In both male and female embryos, the same group of cells has the potential to develop into either the male or female gonads; this tissue is considered bipotential. The *SRY* gene actively recruits other genes that begin to develop the testes, and suppresses genes that are important in female development. As part of this *SRY*-prompted cascade, germ cells in the bipotential gonads differentiate into spermatogonia. Without *SRY*, different genes are expressed, oogonia form, and primordial follicles develop in the primitive ovary.

Soon after the formation of the testis, the Leydig cells begin to secrete testosterone. Testosterone can influence tissues that are bipotential to become male reproductive structures. For example, with exposure to

testosterone, cells that could become either the glans penis or the glans clitoris form the glans penis. Without testosterone, these same cells differentiate into the clitoris.

Sexual differentiation does not begin until the fetal period, during weeks 9–12 ([link]). The internal reproductive structures (for example the uterus, uterine tubes, and part of the vagina in females; and the epididymis, vas deferens, and seminal vesicles in males) form from one of two rudimentary duct systems in the embryo. During male fetal development, the bipotential gonads become the testes and associated epididymis. The presence of testosterone will stimulate the **Wolffian duct** and cause degeneration of the **Müllerian ducts**. The Wolffian ducts will give rise to male reproductive structures such as the vas deferens. The absence of testosterone during female fetal development will stimulate the Müllerian ducts and degeneration of the Wolffian ducts. The Müllerian ducts will give rise to female reproductive structures such as the uterine tubes and uterus. Sexual Differentiation



Differentiation of the male and female reproductive systems does not occur until the fetal period of development.

Note:

Interactive Link Feature



A baby's gender is determined at conception, and the different genitalia of male and female fetuses develop from the same tissues in the embryo. View this <u>animation</u> to see a comparison of the development of structures of the female and male reproductive systems in a growing fetus. Where are the testes located for most of gestational time?

Further Sexual Development Occurs at Puberty

Puberty is the stage of development at which individuals become sexually mature. Though the outcomes of puberty for boys and girls are very different, the hormonal control of the process is very similar. In addition, though the timing of these events varies between individuals, the sequence of changes that occur is predictable for male and female adolescents. As shown in [link], a concerted release of hormones from the hypothalamus (GnRH), the anterior pituitary (LH and FSH), and the gonads (either testosterone or estrogen) is responsible for the maturation of the reproductive systems and the development of **secondary sex characteristics**, which are physical changes that serve auxiliary roles in reproduction.

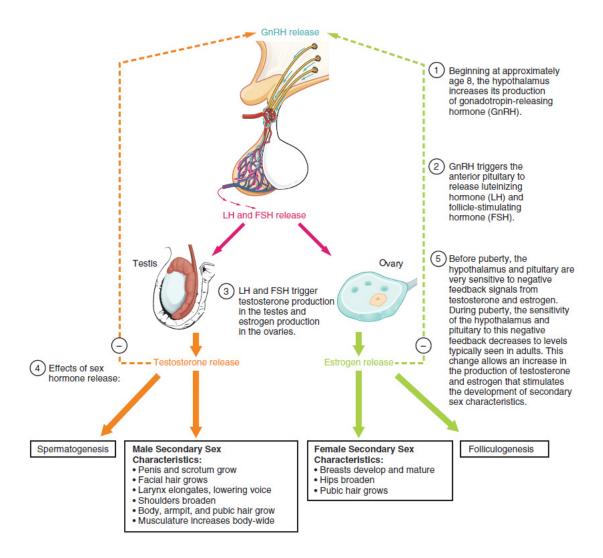
The first changes begin around the age of eight or nine when the production of LH becomes detectable. The release of LH occurs primarily at night during sleep and precedes the physical changes of puberty by several years. In pre-pubertal children, the sensitivity of the negative feedback system in the hypothalamus and pituitary is very high. This means that very low concentrations of androgens or estrogens will negatively feed back onto the

hypothalamus and pituitary, keeping the production of GnRH, LH, and FSH low.

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in girls in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in girls, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In girls who are lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

Hormones of Puberty



During puberty, the release of LH and FSH from the anterior pituitary stimulates the gonads to produce sex hormones in both male and female adolescents.

Signs of Puberty

Different sex steroid hormone concentrations between the sexes also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in [link].

Development of the Secondary Sexual Characteristics	
Male	Female
Increased larynx size and deepening of the voice	Deposition of fat, predominantly in breasts and hips
Increased muscular development	Breast development
Growth of facial, axillary, and pubic hair, and increased growth of body hair	Broadening of the pelvis and growth of axillary and pubic hair

As a girl reaches puberty, typically the first change that is visible is the development of the breast tissue. This is followed by the growth of axillary and pubic hair. A growth spurt normally starts at approximately age 9 to 11, and may last two years or more. During this time, a girl's height can increase 3 inches a year. The next step in puberty is menarche, the start of menstruation.

In boys, the growth of the testes is typically the first physical sign of the beginning of puberty, which is followed by growth and pigmentation of the scrotum and growth of the penis. The next step is the growth of hair, including armpit, pubic, chest, and facial hair. Testosterone stimulates the growth of the larynx and thickening and lengthening of the vocal folds, which causes the voice to drop in pitch. The first fertile ejaculations typically appear at approximately 15 years of age, but this age can vary widely across individual boys. Unlike the early growth spurt observed in females, the male growth spurt occurs toward the end of puberty, at approximately age 11 to 13, and a boy's height can increase as much as 4 inches a year. In some males, pubertal development can continue through the early 20s.

Chapter Review

The reproductive systems of males and females begin to develop soon after conception. A gene on the male's Y chromosome called *SRY* is critical in stimulating a cascade of events that simultaneously stimulate testis development and repress the development of female structures. Testosterone produced by Leydig cells in the embryonic testis stimulates the development of male sexual organs. If testosterone is not present, female sexual organs will develop.

Whereas the gonads and some other reproductive tissues are considered bipotential, the tissue that forms the internal reproductive structures stems from ducts that will develop into only male (Wolffian) or female (Müllerian) structures. To be able to reproduce as an adult, one of these systems must develop properly and the other must degrade.

Further development of the reproductive systems occurs at puberty. The initiation of the changes that occur in puberty is the result of a decrease in sensitivity to negative feedback in the hypothalamus and pituitary gland, and an increase in sensitivity of the gonads to FSH and LH stimulation. These changes lead to increases in either estrogen or testosterone, in female and male adolescents, respectively. The increase in sex steroid hormones leads to maturation of the gonads and other reproductive organs. The initiation of spermatogenesis begins in boys, and girls begin ovulating and menstruating. Increases in sex steroid hormones also lead to the development of secondary sex characteristics such as breast development in girls and facial hair and larynx growth in boys.

Glossary

Müllerian duct

duct system present in the embryo that will eventually form the internal female reproductive structures

puberty

life stage during which a male or female adolescent becomes anatomically and physiologically capable of reproduction

secondary sex characteristics

physical characteristics that are influenced by sex steroid hormones and have supporting roles in reproductive function

Wolffian duct

duct system present in the embryo that will eventually form the internal male reproductive structures

OU Human Physiology: Development Introduction class="introduction" Newborn

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A single fertilized egg develops over the span of nine months into an infant consisting of trillions of cells and capable of surviving outside the womb.

(credit:

"Seattleye"/flickr.com
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Note:

Chapter Objectives

After studying this chapter, you will be able to:

- List and explain the steps involved in fertilization
- Describe the major events in embryonic development
- Describe the major events in fetal development
- Explain what hormones are involved in maintaining pregnancy
- Discuss the adaptations of a woman's body to pregnancy
- Summarize the events leading to labor
- Describe the physiological adjustments that the newborn must make in the first hours of extrauterine life
- Summarize the physiology of lactation

In approximately nine months, a single cell—a fertilized egg—develops into a fully formed infant consisting of trillions of cells with myriad specialized functions. The dramatic changes of fertilization, embryonic development, and fetal development are followed by remarkable adaptations of the newborn to life outside the womb. An offspring's normal development depends upon the appropriate synthesis of structural and functional proteins. This, in turn, is governed by the genetic material inherited from the parental egg and sperm, as well as environmental factors.

OU Human Physiology: Fertilization By the end of this section, you will be able to:

- Describe the obstacles that sperm must overcome to reach an oocyte
- Explain capacitance and its importance in fertilization
- List and explain the steps involved in fertilization
- Explain the mechanisms that prevent polyspermy

Fertilization occurs when a sperm and an oocyte (egg) combine and their nuclei fuse. Because each of these reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell, called a **zygote**, contains all of the genetic material needed to form a human—half from the mother and half from the father.

Transit of Sperm

Fertilization is a numbers game. During ejaculation, hundreds of millions of sperm (spermatozoa) are released into the vagina. Almost immediately, millions of these sperm are overcome by the acidity of the vagina (approximately pH 3.8), and millions more may be blocked from entering the uterus by thick cervical mucus. Of those that do enter, thousands are destroyed by phagocytic uterine leukocytes. Thus, the race into the uterine tubes, which is the most typical site for sperm to encounter the oocyte, is reduced to a few thousand contenders. Their journey—thought to be facilitated by uterine contractions—usually takes from 30 minutes to 2 hours. If the sperm do not encounter an oocyte immediately, they can survive in the uterine tubes for another 3–5 days. Thus, fertilization can still occur if intercourse takes place a few days before ovulation. In comparison, an oocyte can survive independently for only approximately 24 hours following ovulation. Intercourse more than a day after ovulation will therefore usually not result in fertilization.

During the journey, fluids in the female reproductive tract prepare the sperm for fertilization through a process called **capacitation**, or priming. The fluids improve the motility of the spermatozoa. They also deplete cholesterol molecules embedded in the membrane of the head of the sperm,

thinning the membrane in such a way that will help facilitate the release of the lysosomal (digestive) enzymes needed for the sperm to penetrate the oocyte's exterior once contact is made. Sperm must undergo the process of capacitation in order to have the "capacity" to fertilize an oocyte. If they reach the oocyte before capacitation is complete, they will be unable to penetrate the oocyte's thick outer layer of cells.

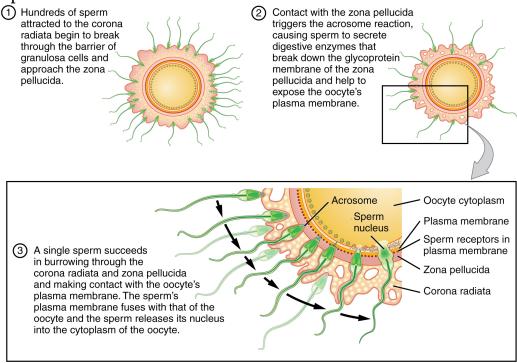
Contact Between Sperm and Oocyte

Upon ovulation, the oocyte released by the ovary is swept into—and along—the uterine tube. Fertilization must occur in the distal uterine tube because an unfertilized oocyte cannot survive the 72-hour journey to the uterus. As you will recall from your study of the oogenesis, this oocyte (specifically a secondary oocyte) is surrounded by two protective layers. The **corona radiata** is an outer layer of follicular (granulosa) cells that form around a developing oocyte in the ovary and remain with it upon ovulation. The underlying **zona pellucida** (pellucid = "transparent") is a transparent, but thick, glycoprotein membrane that surrounds the cell's plasma membrane.

As it is swept along the distal uterine tube, the oocyte encounters the surviving capacitated sperm, which stream toward it in response to chemical attractants released by the cells of the corona radiata. To reach the oocyte itself, the sperm must penetrate the two protective layers. The sperm first burrow through the cells of the corona radiata. Then, upon contact with the zona pellucida, the sperm bind to receptors in the zona pellucida. This initiates a process called the **acrosomal reaction** in which the enzymefilled "cap" of the sperm, called the **acrosome**, releases its stored digestive enzymes. These enzymes clear a path through the zona pellucida that allows sperm to reach the oocyte. Finally, a single sperm makes contact with sperm-binding receptors on the oocyte's plasma membrane ([link]). The plasma membrane of that sperm then fuses with the oocyte's plasma membrane, and the head and mid-piece of the "winning" sperm enter the oocyte interior.

How do sperm penetrate the corona radiata? Some sperm undergo a spontaneous acrosomal reaction, which is an acrosomal reaction not triggered by contact with the zona pellucida. The digestive enzymes released by this reaction digest the extracellular matrix of the corona radiata. As you can see, the first sperm to reach the oocyte is never the one to fertilize it. Rather, hundreds of sperm cells must undergo the acrosomal reaction, each helping to degrade the corona radiata and zona pellucida until a path is created to allow one sperm to contact and fuse with the plasma membrane of the oocyte. If you consider the loss of millions of sperm between entry into the vagina and degradation of the zona pellucida, you can understand why a low sperm count can cause male infertility.

Sperm and the Process of Fertilization



Before fertilization, hundreds of capacitated sperm must break through the surrounding corona radiata and zona pellucida so that one can contact and fuse with the oocyte plasma membrane.

When the first sperm fuses with the oocyte, the oocyte deploys two mechanisms to prevent **polyspermy**, which is penetration by more than one sperm. This is critical because if more than one sperm were to fertilize the

oocyte, the resulting zygote would be a triploid organism with three sets of chromosomes. This is incompatible with life.

The first mechanism is the fast block, which involves a near instantaneous change in sodium ion permeability upon binding of the first sperm, depolarizing the oocyte plasma membrane and preventing the fusion of additional sperm cells. The fast block sets in almost immediately and lasts for about a minute, during which time an influx of calcium ions following sperm penetration triggers the second mechanism, the slow block. In this process, referred to as the **cortical reaction**, cortical granules sitting immediately below the oocyte plasma membrane fuse with the membrane and release zonal inhibiting proteins and mucopolysaccharides into the space between the plasma membrane and the zona pellucida. Zonal inhibiting proteins cause the release of any other attached sperm and destroy the oocyte's sperm receptors, thus preventing any more sperm from binding. The mucopolysaccharides then coat the nascent zygote in an impenetrable barrier that, together with hardened zona pellucida, is called a **fertilization membrane**.

The Zygote

Recall that at the point of fertilization, the oocyte has not yet completed meiosis; all secondary oocytes remain arrested in metaphase of meiosis II until fertilization. Only upon fertilization does the oocyte complete meiosis. The unneeded complement of genetic material that results is stored in a second polar body that is eventually ejected. At this moment, the oocyte has become an ovum, the female haploid gamete. The two haploid nuclei derived from the sperm and oocyte and contained within the egg are referred to as pronuclei. They decondense, expand, and replicate their DNA in preparation for mitosis. The pronuclei then migrate toward each other, their nuclear envelopes disintegrate, and the male- and female-derived genetic material intermingles. This step completes the process of fertilization and results in a single-celled diploid zygote with all the genetic instructions it needs to develop into a human.

Most of the time, a woman releases a single egg during an ovulation cycle. However, in approximately 1 percent of ovulation cycles, two eggs are

released and both are fertilized. Two zygotes form, implant, and develop, resulting in the birth of dizygotic (or fraternal) twins. Because dizygotic twins develop from two eggs fertilized by two sperm, they are no more identical than siblings born at different times.

Much less commonly, a zygote can divide into two separate offspring during early development. This results in the birth of monozygotic (or identical) twins. Although the zygote can split as early as the two-cell stage, splitting occurs most commonly during the early blastocyst stage, with roughly 70–100 cells present. These two scenarios are distinct from each other, in that the twin embryos that separated at the two-cell stage will have individual placentas, whereas twin embryos that form from separation at the blastocyst stage will share a placenta and a chorionic cavity.

Note:

Everyday Connections In Vitro Fertilization

IVF, which stands for in vitro fertilization, is an assisted reproductive technology. In vitro, which in Latin translates to "in glass," refers to a procedure that takes place outside of the body. There are many different indications for IVF. For example, a woman may produce normal eggs, but the eggs cannot reach the uterus because the uterine tubes are blocked or otherwise compromised. A man may have a low sperm count, low sperm motility, sperm with an unusually high percentage of morphological abnormalities, or sperm that are incapable of penetrating the zona pellucida of an egg.

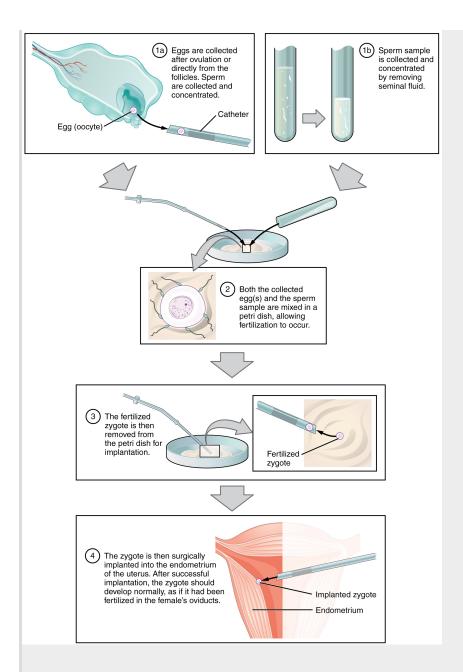
A typical IVF procedure begins with egg collection. A normal ovulation cycle produces only one oocyte, but the number can be boosted significantly (to 10–20 oocytes) by administering a short course of gonadotropins. The course begins with follicle-stimulating hormone (FSH) analogs, which support the development of multiple follicles, and ends with a luteinizing hormone (LH) analog that triggers ovulation. Right before the ova would be released from the ovary, they are harvested using ultrasound-guided oocyte retrieval. In this procedure, ultrasound allows a

physician to visualize mature follicles. The ova are aspirated (sucked out) using a syringe.

In parallel, sperm are obtained from the male partner or from a sperm bank. The sperm are prepared by washing to remove seminal fluid because seminal fluid contains a peptide, FPP (or, fertilization promoting peptide), that—in high concentrations—prevents capacitation of the sperm. The sperm sample is also concentrated, to increase the sperm count per milliliter.

Next, the eggs and sperm are mixed in a petri dish. The ideal ratio is 75,000 sperm to one egg. If there are severe problems with the sperm—for example, the count is exceedingly low, or the sperm are completely nonmotile, or incapable of binding to or penetrating the zona pellucida—a sperm can be injected into an egg. This is called intracytoplasmic sperm injection (ICSI).

The embryos are then incubated until they either reach the eight-cell stage or the blastocyst stage. In the United States, fertilized eggs are typically cultured to the blastocyst stage because this results in a higher pregnancy rate. Finally, the embryos are transferred to a woman's uterus using a plastic catheter (tube). [link] illustrates the steps involved in IVF. **IVF**



In vitro fertilization involves egg collection from the ovaries, fertilization in a petri dish, and the transfer of embryos into the uterus.

IVF is a relatively new and still evolving technology, and until recently it was necessary to transfer multiple embryos to achieve a good chance of a pregnancy. Today, however, transferred embryos are much more likely to implant successfully, so countries that regulate the IVF industry cap the

number of embryos that can be transferred per cycle at two. This reduces the risk of multiple-birth pregnancies.

The rate of success for IVF is correlated with a woman's age. More than 40 percent of women under 35 succeed in giving birth following IVF, but the rate drops to a little over 10 percent in women over 40.

Note:



Go to this <u>site</u> to view resources covering various aspects of fertilization, including movies and animations showing sperm structure and motility, ovulation, and fertilization.

Chapter Review

Hundreds of millions of sperm deposited in the vagina travel toward the oocyte, but only a few hundred actually reach it. The number of sperm that reach the oocyte is greatly reduced because of conditions within the female reproductive tract. Many sperm are overcome by the acidity of the vagina, others are blocked by mucus in the cervix, whereas others are attacked by phagocytic leukocytes in the uterus. Those sperm that do survive undergo a change in response to those conditions. They go through the process of capacitation, which improves their motility and alters the membrane surrounding the acrosome, the cap-like structure in the head of a sperm that contains the digestive enzymes needed for it to attach to and penetrate the oocyte.

The oocyte that is released by ovulation is protected by a thick outer layer of granulosa cells known as the corona radiata and by the zona pellucida, a

thick glycoprotein membrane that lies just outside the oocyte's plasma membrane. When capacitated sperm make contact with the oocyte, they release the digestive enzymes in the acrosome (the acrosomal reaction) and are thus able to attach to the oocyte and burrow through to the oocyte's zona pellucida. One of the sperm will then break through to the oocyte's plasma membrane and release its haploid nucleus into the oocyte. The oocyte's membrane structure changes in response (cortical reaction), preventing any further penetration by another sperm and forming a fertilization membrane. Fertilization is complete upon unification of the haploid nuclei of the two gametes, producing a diploid zygote.

Chapter Review

Hundreds of millions of sperm deposited in the vagina travel toward the oocyte, but only a few hundred actually reach it. The number of sperm that reach the oocyte is greatly reduced because of conditions within the female reproductive tract. Many sperm are overcome by the acidity of the vagina, others are blocked by mucus in the cervix, whereas others are attacked by phagocytic leukocytes in the uterus. Those sperm that do survive undergo a change in response to those conditions. They go through the process of capacitation, which improves their motility and alters the membrane surrounding the acrosome, the cap-like structure in the head of a sperm that contains the digestive enzymes needed for it to attach to and penetrate the oocyte.

The oocyte that is released by ovulation is protected by a thick outer layer of granulosa cells known as the corona radiata and by the zona pellucida, a thick glycoprotein membrane that lies just outside the oocyte's plasma membrane. When capacitated sperm make contact with the oocyte, they release the digestive enzymes in the acrosome (the acrosomal reaction) and are thus able to attach to the oocyte and burrow through to the oocyte's zona pellucida. One of the sperm will then break through to the oocyte's plasma membrane and release its haploid nucleus into the oocyte. The oocyte's membrane structure changes in response (cortical reaction), preventing any further penetration by another sperm and forming a fertilization membrane. Fertilization is complete upon unification of the haploid nuclei of the two gametes, producing a diploid zygote.

Glossary

acrosome

cap-like vesicle located at the anterior-most region of a sperm that is rich with lysosomal enzymes capable of digesting the protective layers surrounding the oocyte

acrosomal reaction

release of digestive enzymes by sperm that enables them to burrow through the corona radiata and penetrate the zona pellucida of an oocyte prior to fertilization

capacitation

process that occurs in the female reproductive tract in which sperm are prepared for fertilization; leads to increased motility and changes in their outer membrane that improve their ability to release enzymes capable of digesting an oocyte's outer layers

corona radiata

in an oocyte, a layer of granulosa cells that surrounds the oocyte and that must be penetrated by sperm before fertilization can occur

cortical reaction

following fertilization, the release of cortical granules from the oocyte's plasma membrane into the zona pellucida creating a fertilization membrane that prevents any further attachment or penetration of sperm; part of the slow block to polyspermy

fertilization

unification of genetic material from male and female haploid gametes

fertilization membrane

impenetrable barrier that coats a nascent zygote; part of the slow block to polyspermy

polyspermy

penetration of an oocyte by more than one sperm

zona pellucida

thick, gel-like glycoprotein membrane that coats the oocyte and must be penetrated by sperm before fertilization can occur

zygote

fertilized egg; a diploid cell resulting from the fertilization of haploid gametes from the male and female lines

OU Human Physiology: Embryonic Development By the end of this section, you will be able to:

- Describe the major events in embryonic development
- Distinguish the stages of embryonic development that occur before implantation
- Describe the process of implantation
- List and describe the four major embryonic membranes
- Describe the major events in embryonic development
- Describe how the placenta is formed and identify its functions
- Explain how an embryo transforms from a flat disc of cells into a three-dimensional shape resembling a human
- Summarize the process of organogenesis

Throughout this chapter, we will express embryonic and fetal ages in terms of weeks from fertilization, commonly called conception. The period of time required for full development of a fetus in utero is referred to as **gestation** (gestare = "to carry" or "to bear"). It can be subdivided into distinct gestational periods. The first 2 weeks of prenatal development are referred to as the pre-embryonic stage. A developing human is referred to as an **embryo** during weeks 3–8, and a **fetus** from the ninth week of gestation until birth. In this section, we'll cover the pre-embryonic and embryonic stages of development, which are characterized by cell division, migration, and differentiation. By the end of the embryonic period, all of the organ systems are structured in rudimentary form, although the organs themselves are either nonfunctional or only semi-functional.

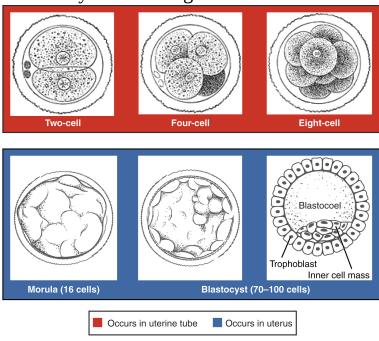
Pre-implantation Embryonic Development

Following fertilization, the zygote and its associated membranes, together referred to as the **conceptus**, continue to be projected toward the uterus by peristalsis and beating cilia. During its journey to the uterus, the zygote undergoes five or six rapid mitotic cell divisions. Although each **cleavage** results in more cells, it does not increase the total volume of the conceptus ([link]). Each daughter cell produced by cleavage is called a **blastomere** (blastos = "germ," in the sense of a seed or sprout).

Approximately 3 days after fertilization, a 16-cell conceptus reaches the uterus. The cells that had been loosely grouped are now compacted and look more like a solid mass. The name given to this structure is the **morula** (morula = "little mulberry"). Once inside the uterus, the conceptus floats freely for several more days. It continues to divide, creating a ball of approximately 100 cells, and consuming nutritive endometrial secretions called uterine milk while the uterine lining thickens. The ball of now tightly bound cells starts to secrete fluid and organize themselves around a fluid-filled cavity, the **blastocoel**. At this developmental stage, the conceptus is referred to as a **blastocyst**. Within this structure, a group of cells forms into an **inner cell mass**, which is fated to become the embryo. The cells that form the outer shell are called **trophoblasts** (trophe = "to feed" or "to nourish"). These cells will develop into the chorionic sac and the fetal portion of the **placenta** (the organ of nutrient, waste, and gas exchange between mother and the developing offspring).

The inner mass of embryonic cells is totipotent during this stage, meaning that each cell has the potential to differentiate into any cell type in the human body. Totipotency lasts for only a few days before the cells' fates are set as being the precursors to a specific lineage of cells.

Pre-Embryonic Cleavages



Pre-embryonic cleavages make use of the

abundant cytoplasm of the conceptus as the cells rapidly divide without changing the total volume.

As the blastocyst forms, the trophoblast excretes enzymes that begin to degrade the zona pellucida. In a process called "hatching," the conceptus breaks free of the zona pellucida in preparation for implantation.

Note:



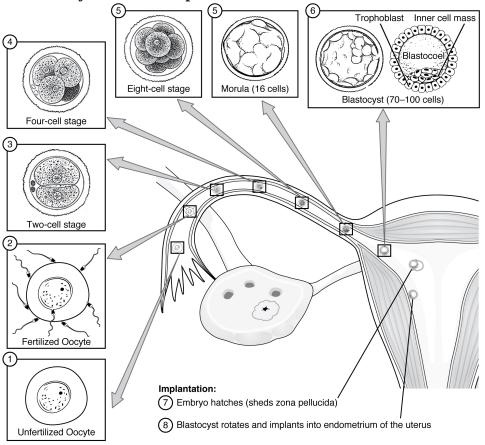
View this time-lapse <u>movie</u> of a conceptus starting at day 3. What is the first structure you see? At what point in the movie does the blastocoel first appear? What event occurs at the end of the movie?

Implantation

At the end of the first week, the blastocyst comes in contact with the uterine wall and adheres to it, embedding itself in the uterine lining via the trophoblast cells. Thus begins the process of **implantation**, which signals the end of the pre-embryonic stage of development ([link]). Implantation can be accompanied by minor bleeding. The blastocyst typically implants in the fundus of the uterus or on the posterior wall. However, if the endometrium is not fully developed and ready to receive the blastocyst, the blastocyst will detach and find a better spot. A significant percentage (50–75 percent) of blastocysts fail to implant; when this occurs, the blastocyst is shed with the endometrium during menses. The high rate of implantation

failure is one reason why pregnancy typically requires several ovulation cycles to achieve.

Pre-Embryonic Development



Ovulation, fertilization, pre-embryonic development, and implantation occur at specific locations within the female reproductive system in a time span of approximately 1 week.

When implantation succeeds and the blastocyst adheres to the endometrium, the superficial cells of the trophoblast fuse with each other, forming the **syncytiotrophoblast**, a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall. In response, the uterine mucosa rebuilds itself and envelops the blastocyst ([link]). The trophoblast secretes **human chorionic gonadotropin (hCG)**, a hormone that directs the corpus luteum to survive, enlarge, and continue

producing progesterone and estrogen to suppress menses. These functions of hCG are necessary for creating an environment suitable for the developing embryo. As a result of this increased production, hCG accumulates in the maternal bloodstream and is excreted in the urine. Implantation is complete by the middle of the second week. Just a few days after implantation, the trophoblast has secreted enough hCG for an at-home urine pregnancy test to give a positive result.

Implantation Endometrium Uterine cavity Uterine mucosa cells 1) The blastocyst digests the uterine mucosa when it initially implants into the endometrium. 2 Eventually, the endometrium grows over and surrounds the embryo, fully securing it to the uterine lining. (3) Implanted embryo continues to grow within endometrium. (Depicted embryo is 7-8 weeks after conception.) Anterior view Lateral view Most common site of implantation

(posterior uterine wall)

During implantation, the trophoblast cells of the blastocyst adhere to the endometrium and digest endometrial cells until it is attached securely.

Most of the time an embryo implants within the body of the uterus in a location that can support growth and development. However, in one to two percent of cases, the embryo implants either outside the uterus (an **ectopic pregnancy**) or in a region of uterus that can create complications for the pregnancy. If the embryo implants in the inferior portion of the uterus, the placenta can potentially grow over the opening of the cervix, a condition call **placenta previa**.

Note:

Disorders of the...

Development of the Embryo

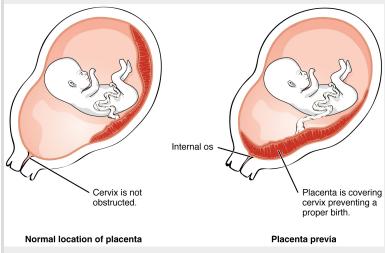
In the vast majority of ectopic pregnancies, the embryo does not complete its journey to the uterus and implants in the uterine tube, referred to as a tubal pregnancy. However, there are also ovarian ectopic pregnancies (in which the egg never left the ovary) and abdominal ectopic pregnancies (in which an egg was "lost" to the abdominal cavity during the transfer from ovary to uterine tube, or in which an embryo from a tubal pregnancy reimplanted in the abdomen). Once in the abdominal cavity, an embryo can implant into any well-vascularized structure—the rectouterine cavity (Douglas' pouch), the mesentery of the intestines, and the greater omentum are some common sites.

Tubal pregnancies can be caused by scar tissue within the tube following a sexually transmitted bacterial infection. The scar tissue impedes the progress of the embryo into the uterus—in some cases "snagging" the embryo and, in other cases, blocking the tube completely. Approximately one half of tubal pregnancies resolve spontaneously. Implantation in a uterine tube causes bleeding, which appears to stimulate smooth muscle contractions and expulsion of the embryo. In the remaining cases, medical or surgical intervention is necessary. If an ectopic pregnancy is detected

early, the embryo's development can be arrested by the administration of the cytotoxic drug methotrexate, which inhibits the metabolism of folic acid. If diagnosis is late and the uterine tube is already ruptured, surgical repair is essential.

Even if the embryo has successfully found its way to the uterus, it does not always implant in an optimal location (the fundus or the posterior wall of the uterus). Placenta previa can result if an embryo implants close to the internal os of the uterus (the internal opening of the cervix). As the fetus grows, the placenta can partially or completely cover the opening of the cervix ([link]). Although it occurs in only 0.5 percent of pregnancies, placenta previa is the leading cause of antepartum hemorrhage (profuse vaginal bleeding after week 24 of pregnancy but prior to childbirth).

Placenta Previa



An embryo that implants too close to the opening of the cervix can lead to placenta previa, a condition in which the placenta partially or completely covers the cervix.

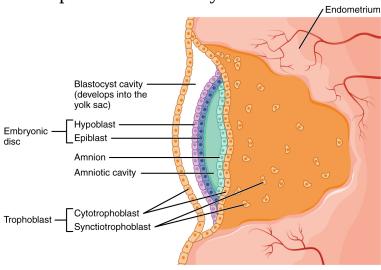
Embryonic Membranes

During the second week of development, with the embryo implanted in the uterus, cells within the blastocyst start to organize into layers. Some grow to

form the extra-embryonic membranes needed to support and protect the growing embryo: the amnion, the yolk sac, the allantois, and the chorion.

At the beginning of the second week, the cells of the inner cell mass form into a two-layered disc of embryonic cells, and a space—the **amniotic cavity**—opens up between it and the trophoblast ([link]). Cells from the upper layer of the disc (the **epiblast**) extend around the amniotic cavity, creating a membranous sac that forms into the **amnion** by the end of the second week. The amnion fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.

Development of the Embryonic Disc



Formation of the embryonic disc leaves spaces on either side that develop into the amniotic cavity and the yolk sac.

On the ventral side of the embryonic disc, opposite the amnion, cells in the lower layer of the embryonic disk (the **hypoblast**) extend into the blastocyst

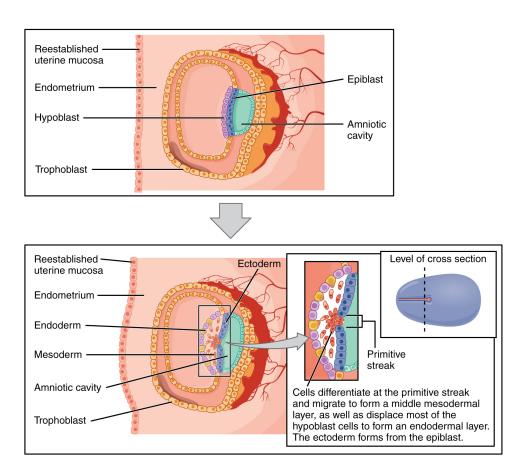
cavity and form a **yolk sac**. The yolk sac supplies some nutrients absorbed from the trophoblast and also provides primitive blood circulation to the developing embryo for the second and third week of development. When the placenta takes over nourishing the embryo at approximately week 4, the yolk sac has been greatly reduced in size and its main function is to serve as the source of blood cells and germ cells (cells that will give rise to gametes). During week 3, a finger-like outpocketing of the yolk sac develops into the **allantois**, a primitive excretory duct of the embryo that will become part of the urinary bladder. Together, the stalks of the yolk sac and allantois establish the outer structure of the umbilical cord.

The last of the extra-embryonic membranes is the **chorion**, which is the one membrane that surrounds all others. The development of the chorion will be discussed in more detail shortly, as it relates to the growth and development of the placenta.

Embryogenesis

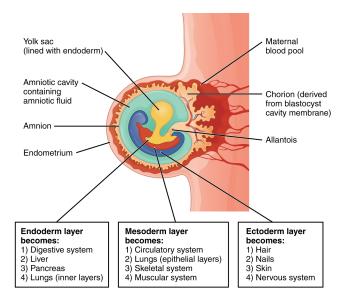
As the third week of development begins, the two-layered disc of cells becomes a three-layered disc through the process of **gastrulation**, during which the cells transition from totipotency to multipotency. The embryo, which takes the shape of an oval-shaped disc, forms an indentation called the **primitive streak** along the dorsal surface of the epiblast. A node at the caudal or "tail" end of the primitive streak emits growth factors that direct cells to multiply and migrate. Cells migrate toward and through the primitive streak and then move laterally to create two new layers of cells. The first layer is the **endoderm**, a sheet of cells that displaces the hypoblast and lies adjacent to the yolk sac. The second layer of cells fills in as the middle layer, or **mesoderm**. The cells of the epiblast that remain (not having migrated through the primitive streak) become the **ectoderm** ([link]).

Germ Layers



Formation of the three primary germ layers occurs during the first 2 weeks of development. The embryo at this stage is only a few millimeters in length.

Each of these germ layers will develop into specific structures in the embryo. Whereas the ectoderm and endoderm form tightly connected epithelial sheets, the mesodermal cells are less organized and exist as a loosely connected cell community. The ectoderm gives rise to cell lineages that differentiate to become the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails. Mesodermal cells ultimately become the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys. The endoderm goes on to form the epithelial lining of the gastrointestinal tract, liver, and pancreas, as well as the lungs ([link]). Fates of Germ Layers in Embryo



Following gastrulation of the embryo in the third week, embryonic cells of the ectoderm, mesoderm, and endoderm begin to migrate and differentiate into the cell lineages that will give rise to mature organs and organ systems in the infant.

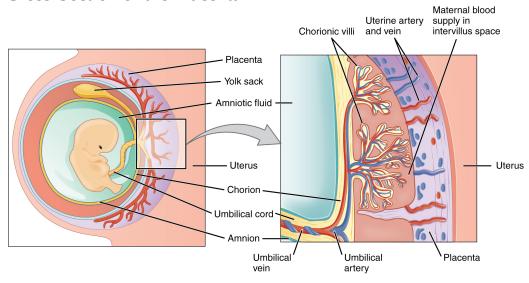
Development of the Placenta

During the first several weeks of development, the cells of the endometrium —referred to as decidual cells—nourish the nascent embryo. During prenatal weeks 4–12, the developing placenta gradually takes over the role of feeding the embryo, and the decidual cells are no longer needed. The mature placenta is composed of tissues derived from the embryo, as well as maternal tissues of the endometrium. The placenta connects to the conceptus via the **umbilical cord**, which carries deoxygenated blood and wastes from the fetus through two umbilical arteries; nutrients and oxygen are carried from the mother to the fetus through the single umbilical vein. The umbilical cord is surrounded by the amnion, and the spaces within the

cord around the blood vessels are filled with Wharton's jelly, a mucous connective tissue.

The maternal portion of the placenta develops from the deepest layer of the endometrium, the decidua basalis. To form the embryonic portion of the placenta, the syncytiotrophoblast and the underlying cells of the trophoblast (cytotrophoblast cells) begin to proliferate along with a layer of extraembryonic mesoderm cells. These form the **chorionic membrane**, which envelops the entire conceptus as the chorion. The chorionic membrane forms finger-like structures called **chorionic villi** that burrow into the endometrium like tree roots, making up the fetal portion of the placenta. The cytotrophoblast cells perforate the chorionic villi, burrow farther into the endometrium, and remodel maternal blood vessels to augment maternal blood flow surrounding the villi. Meanwhile, fetal mesenchymal cells derived from the mesoderm fill the villi and differentiate into blood vessels, including the three umbilical blood vessels that connect the embryo to the developing placenta ([link]).

Cross-Section of the Placenta



In the placenta, maternal and fetal blood components are conducted through the surface of the chorionic villi, but maternal and fetal bloodstreams never mix directly. The placenta develops throughout the embryonic period and during the first several weeks of the fetal period; **placentation** is complete by weeks 14–16. As a fully developed organ, the placenta provides nutrition and excretion, respiration, and endocrine function ([link] and [link]). It receives blood from the fetus through the umbilical arteries. Capillaries in the chorionic villi filter fetal wastes out of the blood and return clean, oxygenated blood to the fetus through the umbilical vein. Nutrients and oxygen are transferred from maternal blood surrounding the villi through the capillaries and into the fetal bloodstream. Some substances move across the placenta by simple diffusion. Oxygen, carbon dioxide, and any other lipid-soluble substances take this route. Other substances move across by facilitated diffusion. This includes water-soluble glucose. The fetus has a high demand for amino acids and iron, and those substances are moved across the placenta by active transport.

Maternal and fetal blood does not commingle because blood cells cannot move across the placenta. This separation prevents the mother's cytotoxic T cells from reaching and subsequently destroying the fetus, which bears "non-self" antigens. Further, it ensures the fetal red blood cells do not enter the mother's circulation and trigger antibody development (if they carry "non-self" antigens)—at least until the final stages of pregnancy or birth. This is the reason that, even in the absence of preventive treatment, an Rh⁻ mother doesn't develop antibodies that could cause hemolytic disease in her first Rh⁺ fetus.

Although blood cells are not exchanged, the chorionic villi provide ample surface area for the two-way exchange of substances between maternal and fetal blood. The rate of exchange increases throughout gestation as the villi become thinner and increasingly branched. The placenta is permeable to lipid-soluble fetotoxic substances: alcohol, nicotine, barbiturates, antibiotics, certain pathogens, and many other substances that can be dangerous or fatal to the developing embryo or fetus. For these reasons, pregnant women should avoid fetotoxic substances. Alcohol consumption by pregnant women, for example, can result in a range of abnormalities referred to as fetal alcohol spectrum disorders (FASD). These include organ and facial malformations, as well as cognitive and behavioral disorders.

Functions of the Placenta				
Nutrition and digestion	Respiration	Endocrine function		
 Mediates diffusion of maternal glucose, amino acids, fatty acids, vitamins, and minerals Stores nutrients during early pregnancy to accommodate increased fetal demand later in pregnancy Excretes and filters fetal nitrogenous wastes into maternal blood 	Mediates maternal-to-fetal oxygen transport and fetal-to-maternal carbon dioxide transport	 Secretes several hormones, including hCG, estrogens, and progesterone, to maintain the pregnancy and stimulate maternal and fetal development Mediates the transmission of maternal hormones into fetal blood and vice versa 		

Placenta



This post-expulsion placenta and umbilical cord (white) are viewed from the fetal side.

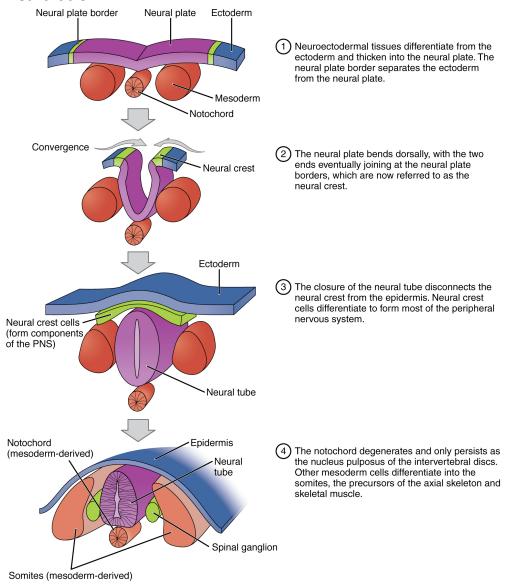
Organogenesis

Following gastrulation, rudiments of the central nervous system develop from the ectoderm in the process of **neurulation** ([link]). Specialized neuroectodermal tissues along the length of the embryo thicken into the **neural plate**. During the fourth week, tissues on either side of the plate fold upward into a **neural fold**. The two folds converge to form the **neural tube**. The tube lies atop a rod-shaped, mesoderm-derived **notochord**, which eventually becomes the nucleus pulposus of intervertebral discs. Block-like structures called **somites** form on either side of the tube, eventually differentiating into the axial skeleton, skeletal muscle, and dermis. During the fourth and fifth weeks, the anterior neural tube dilates and subdivides to form vesicles that will become the brain structures.

Folate, one of the B vitamins, is important to the healthy development of the neural tube. A deficiency of maternal folate in the first weeks of pregnancy can result in neural tube defects, including spina bifida—a birth defect in which spinal tissue protrudes through the newborn's vertebral

column, which has failed to completely close. A more severe neural tube defect is an encephaly, a partial or complete absence of brain tissue.

Neurulation



The embryonic process of neurulation establishes the rudiments of the future central nervous system and skeleton.

The embryo, which begins as a flat sheet of cells, begins to acquire a cylindrical shape through the process of **embryonic folding** ([link]). The

embryo folds laterally and again at either end, forming a C-shape with distinct head and tail ends. The embryo envelops a portion of the yolk sac, which protrudes with the umbilical cord from what will become the abdomen. The folding essentially creates a tube, called the primitive gut, that is lined by the endoderm. The amniotic sac, which was sitting on top of the flat embryo, envelops the embryo as it folds.

Embryonic Folding Transverse section Sagittal section Yolk sac Transverse section Transverse section Yolk sac Transverse section Transverse section Ectoderm Mesoderm Endoderm Amnion Hypoblast

Embryonic folding converts a flat sheet of cells into a hollow, tube-like structure.

Within the first 8 weeks of gestation, a developing embryo establishes the rudimentary structures of all of its organs and tissues from the ectoderm, mesoderm, and endoderm. This process is called **organogenesis**.

Like the central nervous system, the heart also begins its development in the embryo as a tube-like structure, connected via capillaries to the chorionic villi. Cells of the primitive tube-shaped heart are capable of electrical conduction and contraction. The heart begins beating in the beginning of the fourth week, although it does not actually pump embryonic blood until a week later, when the oversized liver has begun producing red blood cells. (This is a temporary responsibility of the embryonic liver that the bone marrow will assume during fetal development.) During weeks 4–5, the eye pits form, limb buds become apparent, and the rudiments of the pulmonary system are formed.

During the sixth week, uncontrolled fetal limb movements begin to occur. The gastrointestinal system develops too rapidly for the embryonic abdomen to accommodate it, and the intestines temporarily loop into the umbilical cord. Paddle-shaped hands and feet develop fingers and toes by the process of apoptosis (programmed cell death), which causes the tissues between the fingers to disintegrate. By week 7, the facial structure is more complex and includes nostrils, outer ears, and lenses ([link]). By the eighth week, the head is nearly as large as the rest of the embryo's body, and all major brain structures are in place. The external genitalia are apparent, but at this point, male and female embryos are indistinguishable. Bone begins to replace cartilage in the embryonic skeleton through the process of ossification. By the end of the embryonic period, the embryo is approximately 3 cm (1.2 in) from crown to rump and weighs approximately 8 g (0.25 oz).

Embryo at 7 Weeks



An embryo at the end of 7 weeks of development is only 10 mm in length, but its developing eyes, limb buds, and tail are already visible. (This embryo was derived from an ectopic pregnancy.)

(credit: Ed Uthman)

Note:



Use this interactive <u>tool</u> to view the process of embryogenesis from the perspective of the conceptus (left panel), as well as fetal development viewed from a maternal cross-section (right panel). Can you identify when neurulation occurs in the embryo?

Chapter Review

As the zygote travels toward the uterus, it undergoes numerous cleavages in which the number of cells doubles (blastomeres). Upon reaching the uterus, the conceptus has become a tightly packed sphere of cells called the morula, which then forms into a blastocyst consisting of an inner cell mass within a fluid-filled cavity surrounded by trophoblasts. The blastocyst implants in the uterine wall, the trophoblasts fuse to form a syncytiotrophoblast, and the conceptus is enveloped by the endometrium. Four embryonic membranes form to support the growing embryo: the amnion, the yolk sac, the allantois, and the chorion. The chorionic villi of the chorion extend into the endometrium to form the fetal portion of the placenta. The placenta supplies the growing embryo with oxygen and nutrients; it also removes carbon dioxide and other metabolic wastes.

Following implantation, embryonic cells undergo gastrulation, in which they differentiate and separate into an embryonic disc and establish three primary germ layers (the endoderm, mesoderm, and ectoderm). Through the process of embryonic folding, the fetus begins to take shape. Neurulation starts the process of the development of structures of the central nervous system and organogenesis establishes the basic plan for all organ systems.

Glossary

allantois

finger-like outpocketing of yolk sac forms the primitive excretory duct of the embryo; precursor to the urinary bladder

amnion

transparent membranous sac that encloses the developing fetus and fills with amniotic fluid

amniotic cavity

cavity that opens up between the inner cell mass and the trophoblast; develops into amnion

blastocoel

fluid-filled cavity of the blastocyst

blastocyst

term for the conceptus at the developmental stage that consists of about 100 cells shaped into an inner cell mass that is fated to become the embryo and an outer trophoblast that is fated to become the associated fetal membranes and placenta

blastomere

daughter cell of a cleavage

chorion

membrane that develops from the syncytiotrophoblast, cytotrophoblast, and mesoderm; surrounds the embryo and forms the fetal portion of the placenta through the chorionic villi

chorionic membrane

precursor to the chorion; forms from extra-embryonic mesoderm cells

chorionic villi

projections of the chorionic membrane that burrow into the endometrium and develop into the placenta

cleavage

form of mitotic cell division in which the cell divides but the total volume remains unchanged; this process serves to produce smaller and smaller cells

conceptus

pre-implantation stage of a fertilized egg and its associated membranes

ectoderm

primary germ layer that develops into the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails

ectopic pregnancy

implantation of an embryo outside of the uterus

embryo

developing human during weeks 3–8

embryonic folding

process by which an embryo develops from a flat disc of cells to a three-dimensional shape resembling a cylinder

endoderm

primary germ layer that goes on to form the gastrointestinal tract, liver, pancreas, and lungs

epiblast

upper layer of cells of the embryonic disc that forms from the inner cell mass; gives rise to all three germ layers

fetus

developing human during the time from the end of the embryonic period (week 9) to birth

gastrulation

process of cell migration and differentiation into three primary germ layers following cleavage and implantation

gestation

in human development, the period required for embryonic and fetal development in utero; pregnancy

human chorionic gonadotropin (hCG)

hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses and secure an environment suitable for the developing embryo

hypoblast

lower layer of cells of the embryonic disc that extend into the blastocoel to form the yolk sac

implantation

process by which a blastocyst embeds itself in the uterine endometrium

inner cell mass

cluster of cells within the blastocyst that is fated to become the embryo

mesoderm

primary germ layer that becomes the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys

morula

tightly packed sphere of blastomeres that has reached the uterus but has not yet implanted itself

neural plate

thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue

neural fold

elevated edge of the neural groove

neural tube

precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium

neurulation

embryonic process that establishes the central nervous system

notochord

rod-shaped, mesoderm-derived structure that provides support for growing fetus

organogenesis

development of the rudimentary structures of all of an embryo's organs from the germ layers

placenta

organ that forms during pregnancy to nourish the developing fetus; also regulates waste and gas exchange between mother and fetus

placenta previa

low placement of fetus within uterus causes placenta to partially or completely cover the opening of the cervix as it grows

placentation

formation of the placenta; complete by weeks 14–16 of pregnancy

primitive streak

indentation along the dorsal surface of the epiblast through which cells migrate to form the endoderm and mesoderm during gastrulation

somite

one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

syncytiotrophoblast

superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall

trophoblast

fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes

umbilical cord

connection between the developing conceptus and the placenta; carries deoxygenated blood and wastes from the fetus and returns nutrients and oxygen from the mother

yolk sac

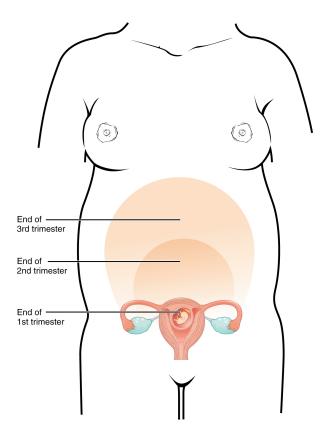
membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure OU Human Physiology: Maternal Changes During Pregnancy, Labor, and Birth

By the end of this section, you will be able to:

- Explain how estrogen, progesterone, and hCG are involved in maintaining pregnancy
- Discuss the adaptations of a woman's body to pregnancy
- Summarize the events leading to labor
- Briefly describe each of the three stages of childbirth

A full-term pregnancy lasts approximately 270 days (approximately 38.5 weeks) from conception to birth. Because it is easier to remember the first day of the last menstrual period (LMP) than to estimate the date of conception, obstetricians set the due date as 284 days (approximately 40.5 weeks) from the LMP. This assumes that conception occurred on day 14 of the woman's cycle, which is usually a good approximation. The 40 weeks of an average pregnancy are usually discussed in terms of three **trimesters**, each approximately 13 weeks. During the second and third trimesters, the pre-pregnancy uterus—about the size of a fist—grows dramatically to contain the fetus, causing a number of anatomical changes in the mother ([link]).

Size of Uterus throughout Pregnancy



The uterus grows throughout pregnancy to accommodate the fetus.

Effects of Hormones

Virtually all of the effects of pregnancy can be attributed in some way to the influence of hormones—particularly estrogens, progesterone, and hCG. During weeks 7–12 from the LMP, the pregnancy hormones are primarily generated by the corpus luteum. Progesterone secreted by the corpus luteum stimulates the production of decidual cells of the endometrium that nourish the blastocyst before placentation. As the placenta develops and the corpus luteum degenerates during weeks 12–17, the placenta gradually takes over as the endocrine organ of pregnancy.

The placenta converts weak androgens secreted by the maternal and fetal adrenal glands to estrogens, which are necessary for pregnancy to progress. Estrogen levels climb throughout the pregnancy, increasing 30-fold by childbirth. Estrogens have the following actions:

- They suppress FSH and LH production, effectively preventing ovulation. (This function is the biological basis of hormonal birth control pills.)
- They induce the growth of fetal tissues and are necessary for the maturation of the fetal lungs and liver.
- They promote fetal viability by regulating progesterone production and triggering fetal synthesis of cortisol, which helps with the maturation of the lungs, liver, and endocrine organs such as the thyroid gland and adrenal gland.
- They stimulate maternal tissue growth, leading to uterine enlargement and mammary duct expansion and branching.

Relaxin, another hormone secreted by the corpus luteum and then by the placenta, helps prepare the mother's body for childbirth. It increases the elasticity of the symphysis pubis joint and pelvic ligaments, making room for the growing fetus and allowing expansion of the pelvic outlet for childbirth. Relaxin also helps dilate the cervix during labor.

The placenta takes over the synthesis and secretion of progesterone throughout pregnancy as the corpus luteum degenerates. Like estrogen, progesterone suppresses FSH and LH. It also inhibits uterine contractions, protecting the fetus from preterm birth. This hormone decreases in late gestation, allowing uterine contractions to intensify and eventually progress to true labor. The placenta also produces hCG. In addition to promoting survival of the corpus luteum, hCG stimulates the male fetal gonads to secrete testosterone, which is essential for the development of the male reproductive system.

The anterior pituitary enlarges and ramps up its hormone production during pregnancy, raising the levels of thyrotropin, prolactin, and adrenocorticotropic hormone (ACTH). Thyrotropin, in conjunction with placental hormones, increases the production of thyroid hormone, which raises the maternal metabolic rate. This can markedly augment a pregnant

woman's appetite and cause hot flashes. Prolactin stimulates enlargement of the mammary glands in preparation for milk production. ACTH stimulates maternal cortisol secretion, which contributes to fetal protein synthesis. In addition to the pituitary hormones, increased parathyroid levels mobilize calcium from maternal bones for fetal use.

Weight Gain

The second and third trimesters of pregnancy are associated with dramatic changes in maternal anatomy and physiology. The most obvious anatomical sign of pregnancy is the dramatic enlargement of the abdominal region, coupled with maternal weight gain. This weight results from the growing fetus as well as the enlarged uterus, amniotic fluid, and placenta. Additional breast tissue and dramatically increased blood volume also contribute to weight gain ([link]). Surprisingly, fat storage accounts for only approximately 2.3 kg (5 lbs) in a normal pregnancy and serves as a reserve for the increased metabolic demand of breastfeeding.

During the first trimester, the mother does not need to consume additional calories to maintain a healthy pregnancy. However, a weight gain of approximately 0.45 kg (1 lb) per month is common. During the second and third trimesters, the mother's appetite increases, but it is only necessary for her to consume an additional 300 calories per day to support the growing fetus. Most women gain approximately 0.45 kg (1 lb) per week.

Contributors to Weight Gain During Pregnancy				
Component	Weight (kg)	Weight (lb)		
Fetus	3.2–3.6	7–8		
Placenta and fetal membranes	0.9–1.8	2–4		

Contributors to Weight Gain During Pregnancy				
Component	Weight (kg)	Weight (lb)		
Amniotic fluid	0.9–1.4	2–3		
Breast tissue	0.9–1.4	2–3		
Blood	1.4	4		
Fat	0.9–4.1	3–9		
Uterus	0.9–2.3	2–5		
Total	10–16.3	22–36		

Changes in Organ Systems During Pregnancy

As the woman's body adapts to pregnancy, characteristic physiologic changes occur. These changes can sometimes prompt symptoms often referred to collectively as the common discomforts of pregnancy.

Digestive and Urinary System Changes

Nausea and vomiting, sometimes triggered by an increased sensitivity to odors, are common during the first few weeks to months of pregnancy. This phenomenon is often referred to as "morning sickness," although the nausea may persist all day. The source of pregnancy nausea is thought to be the increased circulation of pregnancy-related hormones, specifically circulating estrogen, progesterone, and hCG. Decreased intestinal peristalsis may also contribute to nausea. By about week 12 of pregnancy, nausea typically subsides.

A common gastrointestinal complaint during the later stages of pregnancy is gastric reflux, or heartburn, which results from the upward, constrictive pressure of the growing uterus on the stomach. The same decreased peristalsis that may contribute to nausea in early pregnancy is also thought to be responsible for pregnancy-related constipation as pregnancy progresses.

The downward pressure of the uterus also compresses the urinary bladder, leading to frequent urination. The problem is exacerbated by increased urine production. In addition, the maternal urinary system processes both maternal and fetal wastes, further increasing the total volume of urine.

Circulatory System Changes

Blood volume increases substantially during pregnancy, so that by childbirth, it exceeds its preconception volume by 30 percent, or approximately 1–2 liters. The greater blood volume helps to manage the demands of fetal nourishment and fetal waste removal. In conjunction with increased blood volume, the pulse and blood pressure also rise moderately during pregnancy. As the fetus grows, the uterus compresses underlying pelvic blood vessels, hampering venous return from the legs and pelvic region. As a result, many pregnant women develop varicose veins or hemorrhoids.

Respiratory System Changes

During the second half of pregnancy, the respiratory minute volume (volume of gas inhaled or exhaled by the lungs per minute) increases by 50 percent to compensate for the oxygen demands of the fetus and the increased maternal metabolic rate. The growing uterus exerts upward pressure on the diaphragm, decreasing the volume of each inspiration and potentially causing shortness of breath, or dyspnea. During the last several weeks of pregnancy, the pelvis becomes more elastic, and the fetus

descends lower in a process called **lightening**. This typically ameliorates dyspnea.

The respiratory mucosa swell in response to increased blood flow during pregnancy, leading to nasal congestion and nose bleeds, particularly when the weather is cold and dry. Humidifier use and increased fluid intake are often recommended to counteract congestion.

Integumentary System Changes

The dermis stretches extensively to accommodate the growing uterus, breast tissue, and fat deposits on the thighs and hips. Torn connective tissue beneath the dermis can cause striae (stretch marks) on the abdomen, which appear as red or purple marks during pregnancy that fade to a silvery white color in the months after childbirth.

An increase in melanocyte-stimulating hormone, in conjunction with estrogens, darkens the areolae and creates a line of pigment from the umbilicus to the pubis called the linea nigra ([link]). Melanin production during pregnancy may also darken or discolor skin on the face to create a chloasma, or "mask of pregnancy."

Linea Nigra



The linea nigra, a dark medial line running from the umbilicus to

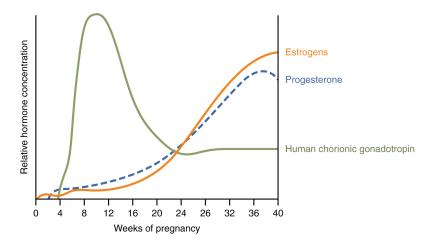
the pubis, forms
during pregnancy and
persists for a few
weeks following
childbirth. The linea
nigra shown here
corresponds to a
pregnancy that is 22
weeks along.

Physiology of Labor

Childbirth, or **parturition**, typically occurs within a week of a woman's due date, unless the woman is pregnant with more than one fetus, which usually causes her to go into labor early. As a pregnancy progresses into its final weeks, several physiological changes occur in response to hormones that trigger labor.

First, recall that progesterone inhibits uterine contractions throughout the first several months of pregnancy. As the pregnancy enters its seventh month, progesterone levels plateau and then drop. Estrogen levels, however, continue to rise in the maternal circulation ([link]). The increasing ratio of estrogen to progesterone makes the myometrium (the uterine smooth muscle) more sensitive to stimuli that promote contractions (because progesterone no longer inhibits them). Moreover, in the eighth month of pregnancy, fetal cortisol rises, which boosts estrogen secretion by the placenta and further overpowers the uterine-calming effects of progesterone. Some women may feel the result of the decreasing levels of progesterone in late pregnancy as weak and irregular peristaltic **Braxton Hicks contractions**, also called false labor. These contractions can often be relieved with rest or hydration.

Hormones Initiating Labor



A positive feedback loop of hormones works to initiate labor.

A common sign that labor will be short is the so-called "bloody show." During pregnancy, a plug of mucus accumulates in the cervical canal, blocking the entrance to the uterus. Approximately 1–2 days prior to the onset of true labor, this plug loosens and is expelled, along with a small amount of blood.

Meanwhile, the posterior pituitary has been boosting its secretion of oxytocin, a hormone that stimulates the contractions of labor. At the same time, the myometrium increases its sensitivity to oxytocin by expressing more receptors for this hormone. As labor nears, oxytocin begins to stimulate stronger, more painful uterine contractions, which—in a positive feedback loop—stimulate the secretion of prostaglandins from fetal membranes. Like oxytocin, prostaglandins also enhance uterine contractile strength. The fetal pituitary also secretes oxytocin, which increases prostaglandins even further. Given the importance of oxytocin and prostaglandins to the initiation and maintenance of labor, it is not surprising that, when a pregnancy is not progressing to labor and needs to be induced, a pharmaceutical version of these compounds (called pitocin) is administered by intravenous drip.

Finally, stretching of the myometrium and cervix by a full-term fetus in the vertex (head-down) position is regarded as a stimulant to uterine contractions. The sum of these changes initiates the regular contractions known as **true labor**, which become more powerful and more frequent with time. The pain of labor is attributed to myometrial hypoxia during uterine contractions.

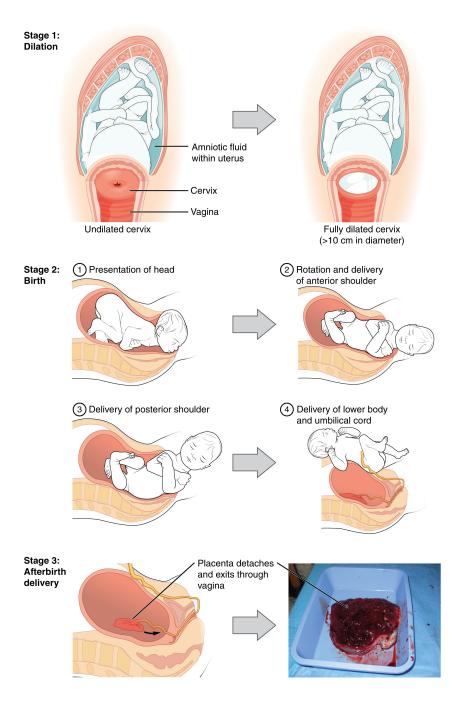
Stages of Childbirth

The process of childbirth can be divided into three stages: cervical dilation, expulsion of the newborn, and afterbirth ([link]).

Cervical Dilation

For vaginal birth to occur, the cervix must dilate fully to 10 cm in diameter—wide enough to deliver the newborn's head. The **dilation** stage is the longest stage of labor and typically takes 6–12 hours. However, it varies widely and may take minutes, hours, or days, depending in part on whether the mother has given birth before; in each subsequent labor, this stage tends to be shorter.

Stages of Childbirth



The stages of childbirth include Stage 1, early cervical dilation; Stage 2, full dilation and expulsion of the newborn; and Stage 3, delivery of the placenta and associated fetal membranes. (The position of the newborn's shoulder is described relative to the mother.)

True labor progresses in a positive feedback loop in which uterine contractions stretch the cervix, causing it to dilate and efface, or become thinner. Cervical stretching induces reflexive uterine contractions that dilate and efface the cervix further. In addition, cervical dilation boosts oxytocin secretion from the pituitary, which in turn triggers more powerful uterine contractions. When labor begins, uterine contractions may occur only every 3–30 minutes and last only 20–40 seconds; however, by the end of this stage, contractions may occur as frequently as every 1.5–2 minutes and last for a full minute.

Each contraction sharply reduces oxygenated blood flow to the fetus. For this reason, it is critical that a period of relaxation occur after each contraction. Fetal distress, measured as a sustained decrease or increase in the fetal heart rate, can result from severe contractions that are too powerful or lengthy for oxygenated blood to be restored to the fetus. Such a situation can be cause for an emergency birth with vacuum, forceps, or surgically by Caesarian section.

The amniotic membranes rupture before the onset of labor in about 12 percent of women; they typically rupture at the end of the dilation stage in response to excessive pressure from the fetal head entering the birth canal.

Expulsion Stage

The **expulsion** stage begins when the fetal head enters the birth canal and ends with birth of the newborn. It typically takes up to 2 hours, but it can last longer or be completed in minutes, depending in part on the orientation of the fetus. The vertex presentation known as the occiput anterior vertex is the most common presentation and is associated with the greatest ease of vaginal birth. The fetus faces the maternal spinal cord and the smallest part of the head (the posterior aspect called the occiput) exits the birth canal first.

In fewer than 5 percent of births, the infant is oriented in the breech presentation, or buttocks down. In a complete breech, both legs are crossed

and oriented downward. In a frank breech presentation, the legs are oriented upward. Before the 1960s, it was common for breech presentations to be delivered vaginally. Today, most breech births are accomplished by Caesarian section.

Vaginal birth is associated with significant stretching of the vaginal canal, the cervix, and the perineum. Until recent decades, it was routine procedure for an obstetrician to numb the perineum and perform an **episiotomy**, an incision in the posterior vaginal wall and perineum. The perineum is now more commonly allowed to tear on its own during birth. Both an episiotomy and a perineal tear need to be sutured shortly after birth to ensure optimal healing. Although suturing the jagged edges of a perineal tear may be more difficult than suturing an episiotomy, tears heal more quickly, are less painful, and are associated with less damage to the muscles around the vagina and rectum.

Upon birth of the newborn's head, an obstetrician will aspirate mucus from the mouth and nose before the newborn's first breath. Once the head is birthed, the rest of the body usually follows quickly. The umbilical cord is then double-clamped, and a cut is made between the clamps. This completes the second stage of childbirth.

Afterbirth

The delivery of the placenta and associated membranes, commonly referred to as the **afterbirth**, marks the final stage of childbirth. After expulsion of the newborn, the myometrium continues to contract. This movement shears the placenta from the back of the uterine wall. It is then easily delivered through the vagina. Continued uterine contractions then reduce blood loss from the site of the placenta. Delivery of the placenta marks the beginning of the postpartum period—the period of approximately 6 weeks immediately following childbirth during which the mother's body gradually returns to a non-pregnant state. If the placenta does not birth spontaneously within approximately 30 minutes, it is considered retained, and the obstetrician may attempt manual removal. If this is not successful, surgery may be required.

It is important that the obstetrician examines the expelled placenta and fetal membranes to ensure that they are intact. If fragments of the placenta remain in the uterus, they can cause postpartum hemorrhage. Uterine contractions continue for several hours after birth to return the uterus to its pre-pregnancy size in a process called **involution**, which also allows the mother's abdominal organs to return to their pre-pregnancy locations. Breastfeeding facilitates this process.

Although postpartum uterine contractions limit blood loss from the detachment of the placenta, the mother does experience a postpartum vaginal discharge called **lochia**. This is made up of uterine lining cells, erythrocytes, leukocytes, and other debris. Thick, dark, lochia rubra (red lochia) typically continues for 2–3 days, and is replaced by lochia serosa, a thinner, pinkish form that continues until about the tenth postpartum day. After this period, a scant, creamy, or watery discharge called lochia alba (white lochia) may continue for another 1–2 weeks.

Chapter Review

Hormones (especially estrogens, progesterone, and hCG) secreted by the corpus luteum and later by the placenta are responsible for most of the changes experienced during pregnancy. Estrogen maintains the pregnancy, promotes fetal viability, and stimulates tissue growth in the mother and developing fetus. Progesterone prevents new ovarian follicles from developing and suppresses uterine contractility.

Pregnancy weight gain primarily occurs in the breasts and abdominal region. Nausea, heartburn, and frequent urination are common during pregnancy. Maternal blood volume increases by 30 percent during pregnancy and respiratory minute volume increases by 50 percent. The skin may develop stretch marks and melanin production may increase.

Toward the late stages of pregnancy, a drop in progesterone and stretching forces from the fetus lead to increasing uterine irritability and prompt labor. Contractions serve to dilate the cervix and expel the newborn. Delivery of the placenta and associated fetal membranes follows.

Glossary

afterbirth

third stage of childbirth in which the placenta and associated fetal membranes are expelled

Braxton Hicks contractions

weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent

dilation

first stage of childbirth, involving an increase in cervical diameter

episiotomy

incision made in the posterior vaginal wall and perineum that facilitates vaginal birth

expulsion

second stage of childbirth, during which the mother bears down with contractions; this stage ends in birth

involution

postpartum shrinkage of the uterus back to its pre-pregnancy volume

lightening

descent of the fetus lower into the pelvis in late pregnancy; also called "dropping"

lochia

postpartum vaginal discharge that begins as blood and ends as a whitish discharge; the end of lochia signals that the site of placental attachment has healed

parturition

childbirth

trimester

division of the duration of a pregnancy into three 3-month terms

true labor

regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time

OU Human Physiology: Lactation By the end of this section, you will be able to:

• Summarize the process of lactation

Lactation is the process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to an infant sucking at the nipple. Breast milk provides ideal nutrition and passive immunity for the infant, encourages mild uterine contractions to return the uterus to its pre-pregnancy size (i.e., involution), and induces a substantial metabolic increase in the mother, consuming the fat reserves stored during pregnancy.

Structure of the Lactating Breast

Mammary glands are modified sweat glands. The non-pregnant and nonlactating female breast is composed primarily of adipose and collagenous tissue, with mammary glands making up a very minor proportion of breast volume. The mammary gland is composed of milk-transporting lactiferous ducts, which expand and branch extensively during pregnancy in response to estrogen, growth hormone, cortisol, and prolactin. Moreover, in response to progesterone, clusters of breast alveoli bud from the ducts and expand outward toward the chest wall. Breast alveoli are balloon-like structures lined with milk-secreting cuboidal cells, or lactocytes, that are surrounded by a net of contractile myoepithelial cells. Milk is secreted from the lactocytes, fills the alveoli, and is squeezed into the ducts. Clusters of alveoli that drain to a common duct are called lobules; the lactating female has 12–20 lobules organized radially around the nipple. Milk drains from lactiferous ducts into lactiferous sinuses that meet at 4 to 18 perforations in the nipple, called nipple pores. The small bumps of the areola (the darkened skin around the nipple) are called Montgomery glands. They secrete oil to cleanse the nipple opening and prevent chapping and cracking of the nipple during breastfeeding.

The Process of Lactation

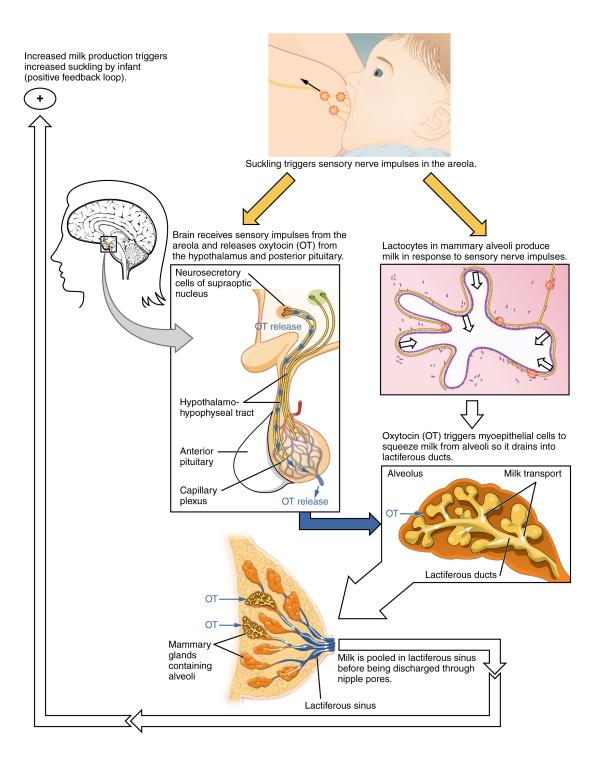
The pituitary hormone **prolactin** is instrumental in the establishment and maintenance of breast milk supply. It also is important for the mobilization of maternal micronutrients for breast milk.

Near the fifth week of pregnancy, the level of circulating prolactin begins to increase, eventually rising to approximately 10–20 times the pre-pregnancy concentration. We noted earlier that, during pregnancy, prolactin and other hormones prepare the breasts anatomically for the secretion of milk. The level of prolactin plateaus in late pregnancy, at a level high enough to initiate milk production. However, estrogen, progesterone, and other placental hormones inhibit prolactin-mediated milk synthesis during pregnancy. It is not until the placenta is expelled that this inhibition is lifted and milk production commences.

After childbirth, the baseline prolactin level drops sharply, but it is restored for a 1-hour spike during each feeding to stimulate the production of milk for the next feeding. With each prolactin spike, estrogen and progesterone also increase slightly.

When the infant suckles, sensory nerve fibers in the areola trigger a neuroendocrine reflex that results in milk secretion from lactocytes into the alveoli. The posterior pituitary releases oxytocin, which stimulates myoepithelial cells to squeeze milk from the alveoli so it can drain into the lactiferous ducts, collect in the lactiferous sinuses, and discharge through the nipple pores. It takes less than 1 minute from the time when an infant begins suckling (the latent period) until milk is secreted (the let-down). [link] summarizes the positive feedback loop of the let-down reflex.

Let-Down Reflex



A positive feedback loop ensures continued milk production as long as the infant continues to breastfeed.

The prolactin-mediated synthesis of milk changes with time. Frequent milk removal by breastfeeding (or pumping) will maintain high circulating prolactin levels for several months. However, even with continued breastfeeding, baseline prolactin will decrease over time to its prepregnancy level. In addition to prolactin and oxytocin, growth hormone, cortisol, parathyroid hormone, and insulin contribute to lactation, in part by facilitating the transport of maternal amino acids, fatty acids, glucose, and calcium to breast milk.

Changes in the Composition of Breast Milk

In the final weeks of pregnancy, the alveoli swell with **colostrum**, a thick, yellowish substance that is high in protein but contains less fat and glucose than mature breast milk ([link]). Before childbirth, some women experience leakage of colostrum from the nipples. In contrast, mature breast milk does not leak during pregnancy and is not secreted until several days after childbirth.

Compositions of Human Colostrum, Mature Breast Milk, and
Cow's Milk (g/L)

	Human colostrum	Human breast milk	Cow's milk*
Total protein	23	11	31
Immunoglobulins	19	0.1	1
Fat	30	45	38
Lactose	57	71	47

Compositions of Human Colostrum, Mature Breast Milk, and Cow's Milk (g/L)

	Human colostrum	Human breast milk	Cow's milk*
Calcium	0.5	0.3	1.4
Phosphorus	0.16	0.14	0.90
Sodium	0.50	0.15	0.41

^{*}Cow's milk should never be given to an infant. Its composition is not suitable and its proteins are difficult for the infant to digest.

Colostrum is secreted during the first 48–72 hours postpartum. Only a small volume of colostrum is produced—approximately 3 ounces in a 24-hour period—but it is sufficient for the newborn in the first few days of life. Colostrum is rich with immunoglobulins, which confer gastrointestinal, and also likely systemic, immunity as the newborn adjusts to a nonsterile environment.

After about the third postpartum day, the mother secretes transitional milk that represents an intermediate between mature milk and colostrum. This is followed by mature milk from approximately postpartum day 10 (see [link]). As you can see in the accompanying table, cow's milk is not a substitute for breast milk. It contains less lactose, less fat, and more protein and minerals. Moreover, the proteins in cow's milk are difficult for an infant's immature digestive system to metabolize and absorb.

The first few weeks of breastfeeding may involve leakage, soreness, and periods of milk engorgement as the relationship between milk supply and infant demand becomes established. Once this period is complete, the mother will produce approximately 1.5 liters of milk per day for a single infant, and more if she has twins or triplets. As the infant goes through growth spurts, the milk supply constantly adjusts to accommodate changes in demand. A woman can continue to lactate for years, but once

breastfeeding is stopped for approximately 1 week, any remaining milk will be reabsorbed; in most cases, no more will be produced, even if suckling or pumping is resumed.

Mature milk changes from the beginning to the end of a feeding. The early milk, called **foremilk**, is watery, translucent, and rich in lactose and protein. Its purpose is to quench the infant's thirst. **Hindmilk** is delivered toward the end of a feeding. It is opaque, creamy, and rich in fat, and serves to satisfy the infant's appetite.

During the first days of a newborn's life, it is important for meconium to be cleared from the intestines and for bilirubin to be kept low in the circulation. Recall that bilirubin, a product of erythrocyte breakdown, is processed by the liver and secreted in bile. It enters the gastrointestinal tract and exits the body in the stool. Breast milk has laxative properties that help expel meconium from the intestines and clear bilirubin through the excretion of bile. A high concentration of bilirubin in the blood causes jaundice. Some degree of jaundice is normal in newborns, but a high level of bilirubin—which is neurotoxic—can cause brain damage. Newborns, who do not yet have a fully functional blood—brain barrier, are highly vulnerable to the bilirubin circulating in the blood. Indeed, hyperbilirubinemia, a high level of circulating bilirubin, is the most common condition requiring medical attention in newborns. Newborns with hyperbilirubinemia are treated with phototherapy because UV light helps to break down the bilirubin quickly.

Chapter Review

The lactating mother supplies all the hydration and nutrients that a growing infant needs for the first 4–6 months of life. During pregnancy, the body prepares for lactation by stimulating the growth and development of branching lactiferous ducts and alveoli lined with milk-secreting lactocytes, and by creating colostrum. These functions are attributable to the actions of several hormones, including prolactin. Following childbirth, suckling triggers oxytocin release, which stimulates myoepithelial cells to squeeze milk from alveoli. Breast milk then drains toward the nipple pores to be consumed by the infant. Colostrum, the milk produced in the first

postpartum days, provides immunoglobulins that increase the newborn's immune defenses. Colostrum, transitional milk, and mature breast milk are ideally suited to each stage of the newborn's development, and breastfeeding helps the newborn's digestive system expel meconium and clear bilirubin. Mature milk changes from the beginning to the end of a feeding. Foremilk quenches the infant's thirst, whereas hindmilk satisfies the infant's appetite.

Glossary

colostrum

thick, yellowish substance secreted from a mother's breasts in the first postpartum days; rich in immunoglobulins

foremilk

watery, translucent breast milk that is secreted first during a feeding and is rich in lactose and protein; quenches the infant's thirst

hindmilk

opaque, creamy breast milk delivered toward the end of a feeding; rich in fat; satisfies the infant's appetite

lactation

process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to sucking at the nipple

let-down reflex

release of milk from the alveoli triggered by infant suckling

prolactin

pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk